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GONOCOCCIC PERITONITIS OF THE UPPER PART OF THE ABDOMEN IN YOUNG WOMEN

(Phrenic Reaction, or Subcostal Syndrome of Stajano; Fitz-Hugh-Curtis Syndrome)

Report of Cases of Three Patients Treated Successfully with Penicillin
and a Summary of the Literature

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PERITONITIS of the upper part of the abdomen in young women occurring during the course of gonorrhea was first described as a definite syndrome in 1919 by Carlos Stajano, in a paper read before the Society of Obstetrics and Gynecology of Montevideo, Uruguay. In his subsequent publications¹ the clinical features of the acute stage of the disease were completely and graphically depicted. Little information of a clinical nature has been added since. Unfortunately, none of his work, printed in Spanish and French, was widely circulated in the United States. Hence it was not until 1930 that Curtis² called attention to the frequent coexistence of gonococcic salpingitis and "violin string" adhesions between the anterior surface of the liver and the anterior abdominal wall discovered at operation—conditions indicating, presumably, a chronic, healing or healed perihepatitis. Fitz-Hugh, in 1934,³ described 3 cases in the acute stage, including 1 in which laparotomy was performed; in smears of the draining secretions from the wound gram-negative intracellular diplococci were seen. Since then numerous articles have appeared in the literature, and the clinical entity has been well documented.

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

1. (a) Stajano, C.: La reacción frénica en ginecología, *Semana méd.* **27**: 243-248 (Aug. 19) 1920; (b) Réaction phrénique et infection génitale, *Gynéc. et obst.* **6**:44-48 (July) 1922. (c) Stajano, C., and Pouey, E.: Las reacciones del peritoneo supracelíaco de origen genital: Las reacciones precoces. *Casuística, An. Fac. de med. de Montevideo* **5**:202 (May-June) 1920; cited by Rodríguez López.^{10d} (d) Stajano, C.: La reacción frénica en ginecología: Fisiopatología y mecanismo de la reacción subcostal, *ibid.* **5**:722 (Nov.-Dec.) 1920; cited by Rodríguez López.^{10d}

2. Curtis, A. H.: A Cause of Adhesions in the Right Upper Quadrant, *J. A. M. A.* **94**:1221-1222 (April 19) 1930.

3. Fitz-Hugh, T., Jr.: Acute Gonococcic Peritonitis of the Right Upper Quadrant in Women, *J. A. M. A.* **102**:2094-2096 (June 23) 1934.

The purpose of this paper is to report 3 typical cases of gonococcic perihepatitis. The internists and surgeons who saw the patients in consultation were all reluctant to accept the diagnosis. Since the syndrome is apparently not well known, the salient features of the disease will be summarized from the literature and from these cases.

All 3 patients were treated with penicillin and recovered rapidly. Although previous reports of therapy of this particular type of lesion with penicillin have not appeared, the results were to be anticipated in view of repeated demonstrations of its efficacy in other forms of gonococcic infections.

CLINICAL SYNDROME

No cases of gonococcic perihepatitis in men have been reported. The disease occurs chiefly, but not exclusively, in young women, since it is between the ages of 20 and 35 that gonorrhea is most prevalent.

Invariably women in whom the syndrome develops have had an antecedent gonococcic infection, sometimes as far in the past as five years before. At times the peritonitis may have its onset concomitantly with, or may actually seem to precede, pelvic extension of the disease (*las reacciones precoces*).^{1c} The initial infection may have been recognized and treated, often inadequately. Incomplete treatment is less common now than formerly, especially when penicillin is used, and reinfections are more frequent. Often it will be impossible to elicit the usual symptoms of gonorrhea because in the female it may assume a latent and entirely asymptomatic form. However, on direct questioning the history will frequently be obtained of menorrhagia or dysmenorrhea, burning on urination, vaginal discharge or vague pain in the lower part of the abdomen during the few days or weeks preceding occurrence of frank symptoms of peritonitis.

The onset is usually dramatic. There is the sudden occurrence of excruciating sharp pain in the upper part of the abdomen, usually on the right side, most intense anteriorly under the rib margins and often referred to the top of the corresponding shoulder. It is of the "pleuritic" type, exaggerated by deep breathing, coughing or laughing and by movements of the trunk, such as bending and walking. The pain may be on the left side or bilateral at the onset⁴ and may alternately afflict one side and then the other (*la bascula diafragmatica pelviana*).¹ It may be referred to the inside of the arm as well as to the shoulder.¹ It may be most acute posteriorly, in the lumbar or costovertebral region,⁵ or laterally, over the lower ribs. Hiccup may be troublesome. Nausea

4. Claudian, I., and Florian, I.: Le syndrome abdominal supérieur et pleuro-diaphragmatique aigu au cours des annexites gonococciques; *Ann. de méd.* **43**: 62-72 (Jan.) 1938. (b) Footnote 1.

5. Hinton, J. W.: Hepatodiaphragmatic Adhesions as a Cause of Upper Abdominal Pain, *J. A. M. A.* **95**:1744-1745 (Dec. 6) 1930.

is of frequent occurrence, but vomiting follows less often. When symptoms are present in the lower part of the abdomen, they are usually worse on the side of the phrenic reaction, but their intensity is such that they are usually overshadowed by the more acute process in the upper part of the abdomen. Chills, fever, sweats and headache may be present.

It has been repeatedly recognized that trauma to inflamed pelvic organs, in the form of surgical procedures,^{1d} gynecologic examination, intercourse or douching, may precipitate the development of this complication. One of the most frequently observed types of reaction in the experience of Stajano^{1d} was the postoperative variety. Patients in whom pelvic operations were undertaken before the inflammatory processes had completely subsided and whose natural barriers to the spread of infection beyond the pelvis were ruptured often experienced the phrenic reaction ten to twelve hours postoperatively. Stajano described a patient who had a bilateral phrenic reaction, who was operated on and who underwent a unilateral postoperative reaction; the course of the latter type of complication differed in no way from that of the former.

The physical examination discloses an acutely ill but not prostrated patient. The temperature is usually somewhat elevated, although rarely above 102 F. unless there are additional complications present. There is pronounced tenderness and muscular spasm at the site of greatest intensity of pain, usually in the right upper abdominal quadrant, indicating an underlying peritoneal inflammatory process. As further evidence of this, occasionally a friction rub⁶ is heard at the anterior costal margin, which has been described as similar to the "crunching of new snow."^{6a} The suspicion of preceding gonorrhea aroused by the finding of slight or moderate tenderness in the lower part of the abdomen is confirmed when other evidences of gonococcic infection—inflammation of Skene's glands or of the glands of Bartholin, urethritis, cervicitis or salpingitis—are discovered.

Slight dulness to percussion at the bases of the lungs posteriorly has often been noted, and small pleural effusions,⁴ confirmed by aspiration of small quantities of fluid, occur not uncommonly. Slight or moderate tenderness over the costovertebral angle is not unusual.

Other stigmas of gonococcic infection, such as arthritis, tenosynovitis (case 2) or keratosis blennorrhagica, may be present.

6. (a) Fitz-Hugh, T., Jr.: Acute Gonococcic Perihepatitis: A New Syndrome of Right Upper Quadrant Abdominal Pain in Young Women, *Rev. Gastroenterol.* **3**:125-131 (June) 1936. (b) Hahn, T. F.: Gonococcal Peritonitis of the Upper Right Quadrant, *J. Florida M. A.* **25**:73-75 (Aug.) 1938. Footnote 4. Fitz-Hugh.³

Culture of the cervical or urethral secretions under proper conditions invariably yields gonococci. This observation is often not confirmed by examination of stained smears, no matter how painstakingly carried out. Leukocytosis is the rule, although the total count is usually not elevated above 15,000 white cells per cubic millimeter of blood; complications may cause it to be increased above this figure. The gonococcus complement fixation test, carried out on the blood, gives positive results in a variable percentage of cases, from 33 per cent³ to 100 per cent;⁷ hence, it is of diagnostic value only when the result is positive. Fluid aspirated from the pleural cavity is sterile and may vary widely in content of cells.^{4a} Especially in patients in whom there occurs perihepatitis, a very slight, transient elevation of bilirubin content of the blood may be found during the height of the process (case 2). A slightly icteric tinge has been noted^{6a} uncommonly. Duodenal drainages were performed on 18 patients in one series,⁷ with uniformly negative results.

Roentgenologic visualization of the gallbladder by means of radio-paque dye reveals a normally functioning organ, without stones, in nearly every instance.⁷ However, especially if the procedure is carried out when the inflammatory process is still acute, a nonfilling gallbladder may occasionally be found, as in Fitz-Hugh's³ first case. This is not surprising in view of the dense pericholecystic adhesions reported in some instances,⁷ which could easily interfere with normal vesical function at an early stage in the course of the inflammation.

The roentgenogram of the chest is usually normal except for some elevation of the diaphragm on the affected side. In 1 case, paresis of the diaphragm on one side was seen fluoroscopically by Stajano.^{1a} The roentgenogram of the abdomen reveals normal conditions, no radio-paque stones being visible. There may be an increased amount of gas in the colon.

INCIDENCE

Opinions vary as to the frequency of occurrence of this complication of gonorrhea. Figures are available which differ from a fraction of 1 per cent of all infections, quoted by Brunet,⁸ to 10 per cent of all women with "pelvic inflammatory disease," estimated by Maxwell (quoted by Redewill).⁹ A survey of the published material on the

7. Boller, R., and Makrycostas, K.: Die chronische Pericholecystitis bei gonorrhoeischen Adnexerkrankungen und ihre Behandlung, *Klin. Wchnschr.* **13**: 1180-1183 (Aug. 18) 1934.

8. Brunet, W. M.: Acute Gonococcal Perihepatitis, with Report of Five Cases, *Am. J. Obst. & Gynec.* **39**:481-485 (March) 1940.

9. Redewill, F. H.: Acute Gonococcic Perihepatitis: Abdominal Pain in the Upper Right Quadrant in Young Women, *Urol. & Cutan. Rev.* **41**:685-692 (Oct.) 1937.

subject¹⁰ shows that descriptions of 129 cases have been reported. There is general agreement that this relatively small figure of total reported cases imparts a false impression of the rarity of the syndrome and that it is much commoner than generally believed. This is undoubtedly true, since many cases are diagnosed incorrectly while others escape attention because of the commonly transitory nature of the pain. Peritonitis of the upper part of the abdomen is a not uncommon sequel to gonococcic salpingitis.

PATHOLOGY AND PATHOGENESIS

Although gonococci have not actually been cultured from material taken directly from the subphrenic space at operation, there can be little doubt that they are present. Thus, in Fitz-Hugh's³ case, typical gram-negative intracellular diplococci were seen in smears of the pus draining from the wound. Mauro^{10g} cultured the organisms likewise from the secretions draining through the wound in the upper part of the abdomen.

That the subphrenic process is in the acute stage a true infective peritonitis, not "a mere congestion of the phrenic serosa,"^{1a,d} a sort of "sympathetic" reaction to pelvic peritonitis, as Stajano implied, has been demonstrated by Fitz-Hugh, Mauro, Curtis and others. Fitz-Hugh,³ whose patient was operated on after a ten day period during which her symptoms subsided, noted at laparotomy that a "localized fairly dry peritonitis involved the anterior surface and edge of the liver and the adjacent peritoneal surface of the diaphragm and the anterior abdominal wall. The peritoneum in these areas was injected and had the appearance of salt sprinkled on a moist surface." In Mauro's^{10g} case, at operation also, "the surface of the liver was covered with deposits of fibrin of considerable size." Symptoms were of approximately twenty-four hours' duration. Presumably, this acute inflammatory reaction subsides in a few weeks and leaves the "violin string" adhesions in the same location, either between the liver and diaphragm or anterior wall of the abdomen² or surrounding the gallbladder.⁷ This residue of

10. (a) Curtis, A. H.: Adhesions of the Anterior Surface of the Liver, *J. A. M. A.* **99**:2010-2012 (Dec. 10) 1932. (b) Bearse, C.: Gonorrheal Salpingitis and Perihepatic Adhesions, *ibid.* **97**:1385 (Nov. 7) 1931. (c) Hertz, C. S.: Acute Gonococcic Perihepatitis, *Proc. Staff Meet., Mayo Clin.* **13**:577-581 (Sept. 14) 1938. (d) Rodríguez López, M. B.: El síndrome subcostal y de reacción frénica del profesor doctor Carlos Stajano en las anexitis gonocóccicas, *Arch. urug. de med., cir. y especialid.* **16**:313-319 (April) 1940. (e) Hudgins, A. P.: Acute Gonococcic Perihepatitis, *West Virginia M. J.* **37**:77-79 (Feb.) 1941. (f) Steinberg, B.: *Infections of the Peritoneum*, New York, Paul B. Hoeber, Inc., 1944, pp. 231-241. (g) Curtis.² Hinton.⁵ Footnote 6. Boller and Makrycostas.⁷ Brunet.⁸ Redewill.⁹ Mauro, E.: Le syndrome abdominal droit supérieur au cours des annexites gonococciques (syndrome de Fitz-Hugh), *Presse méd.* **46**:1919-1921 (Dec. 28) 1938.

adhesions may persist indefinitely. Recently, an 80 year old woman who died after a pulmonary infection was seen at autopsy to have typical subphrenic adhesions along with healed salpingitis and evidences of healed pelvic peritonitis. One can only estimate their duration, but it is probable that they had remained twenty or more years.

There appears to be almost no tendency toward abscess formation in the subdiaphragmatic space following its invasion by the gonococcus. The subphrenic abscess reported by Scott¹¹ is a distinct rarity. In this case, too, the diagnosis was made by smear, and cultures of the pus from the abscess were sterile. However, similar organisms were also seen in the cervical smear. Of a series of 3,608 collected and personal cases of subphrenic abscesses (Ochsner and De Bakey¹²) in only 54 (1.5 per cent) could the process be said to have its origin in the female genitalia. It was not possible to say how many of these were of gonococcic origin. Thus, the course of the disease is different from that of infections of the same region due to colon bacilli, streptococci and *Staphylococcus aureus*, the major causes of subphrenic abscesses. However, even when the latter organisms are present, abscess formation does not occur in every case of subphrenic infection. Ochsner and De Bakey¹² said: "In our experience approximately 70 per cent of subphrenic infections which are diagnosed from the clinical manifestations subside without proceeding to suppuration." Neuhof,¹³ Lee¹⁴ and Clendening¹⁵ described cases in which spontaneous recovery was the conspicuous feature.

From study of the biopsy material in his first case, Fitz-Hugh^{6a} was able to state that "the inflammation of the liver capsule may extend into the outer zone of the liver parenchyma which, in one of my sections from case 1, showed some small islands of regenerating liver cells surrounded by strands of inflammatory connective tissue dipping in from the capsule." It may be, then, that the mild, transient and usually subclinical icteric states occasionally seen (case 2) can be accounted for by actual peripheral hepatitis.

Much has been written about the route of extension of the infection from the pelvis to the subphrenic spaces, whether via the paracolic

11. Scott, G. D.: Subdiaphragmatic Gonorrheal Abscess, *J. A. M. A.* **96**: 1681-1682 (May 16) 1931.

12. Ochsner, A., and De Bakey, M.: Subphrenic Abscess: Collective Review and an Analysis of 3,608 Collected and Personal Cases, *Internat. Abstr. Surg.* **66**:426-438 (May) 1938.

13. Neuhof, H.: Non-Suppurative Subphrenic Peritonitis Complicating Appendicitis, *Surg., Gynec. & Obst.* **14**:231-246 (March) 1912.

14. Lee, R. I.: Subdiaphragmatic Inflammation with a Syndrome of Physical Signs and Spontaneous Recovery Without Suppuration, *J. A. M. A.* **64**:1307-1310 (April 17) 1915.

15. Clendening, L.: Subphrenic Infection: Cases Illustrative of the Different Forms of This Condition, *M. Clin. North America* **7**:1147-1167 (Jan.) 1924.

gutter or through the retroperitoneal lymphatics. While there is not enough evidence to settle the question—if, indeed, there is only one method in all cases—it may be said that it is the rule to encounter tenderness in the middle part of the abdomen laterally, indicating inflammation of the peritoneum between the pelvis and diaphragm. Thus, Miller,¹⁶ on several occasions when he operated before complete subsidence of the infectious process, noted that “considerable peritoneal fluid was present and granular exudate, agglutinating several coils of the intestine, was found as high up as the level of the umbilicus.” At least in some instances, then, there is direct extension rather than metastasis.

DIAGNOSIS

When one is presented with the clinical picture previously described, especially in a young woman, the diagnosis can be made with a high degree of certainty by merely establishing the presence of gonococci in the urethra or cervix. That this decision should be made on the basis of culture, and not of smears alone, cannot be too strongly emphasized. Thus, in 2 of the 3 cases reported herein smears were repeatedly negative or inconclusive although the organisms were easily cultured in large numbers. It should be reiterated that gonorrhea in women is often relatively asymptomatic, hence extremely difficult to detect clinically. The most reliable method of diagnosis is by culture of the causative organism.

It has been the experience of workers in the bacteriology laboratory where my work is done that the growth of gonococci has not been difficult on beef heart infusion tryptose agar with 10 per cent defibrinated sheep blood employed routinely for blood agar plates. For use in isolating the organism from clinical material (pus) the p_H should be adjusted to between 7.6 and 7.8 rather than 7.2, the reaction commonly employed in growth of stock cultures. The plates should be incubated in a candle jar or other device for attaining approximately 2 per cent concentration of carbon dioxide in the surrounding atmosphere.

DIFFERENTIAL DIAGNOSIS

The most frequently encountered diagnostic problem is differentiation of gonococcic peritonitis from acute cholecystitis. In the acute stage there may be a nonfilling gallbladder, which further confuses the picture. When the inflammation assumes the form of pericholecystitis, differentiation may be impossible. It should be remembered that gallstones are uncommon before the age of 30, especially in women who are not fat, and that pain is not often referred to the top of the shoulder and the root of the neck via the phrenic nerve unless the inflammation is subphrenic rather than subhepatic. Other abdominal conditions from

¹⁶ Miller, H., in discussion on Curtis.^{10a}

which this disease must be differentiated include ruptured peptic ulcer, appendicitis with subphrenic abscess and other forms of peritonitis. If the pain is greatest posteriorly, as in Hinton's⁵ case, pyelitis, nephrolithiasis or perinephric abscess must be considered. In the chest pneumonia of the lower lobe of the lung and pleurisy due to other causes may have to be ruled out. Herpes zoster and epidemic pleurodynia are other possibilities.

An accurate diagnosis is important, especially in ruling out those diseases requiring surgical intervention, for not only is such interference unnecessary but it may actually be harmful. Presence of other complications of gonococcal infection, such as arthritis or tenosynovitis, may simplify the process of differentiation. A past history of any venereal disease is obviously an important indication of the possibilities of multiple infections, of which gonorrhea may be one.

COURSE AND PROGNOSIS; TREATMENT

There have been no deaths reported as resulting from this type of gonococcal peritonitis. The usual course when it is untreated is slow subsidence of the acute pain to a dull ache which gradually disappears, the whole process requiring from one to four weeks. One of the astonishing features is the rapid decline of symptoms and the commonly transitory nature of the acute process without any treatment. However, in such instances recurrences are frequent. After the inflammation has abated and the adhesions have formed there is no reason to believe that pain will persist unless, of course, as often happens, there is a recurrence.

The therapy which has been employed in the past has been that most popular at the time the cases were described. Thus, gonococcus vaccine, hyperpyrexia and the various sulfonamide compounds have been used with varying success. At the present time penicillin is the drug of choice; with doses of 20,000 units administered every three hours intramuscularly, there is almost complete relief of symptoms after twenty-four hours of treatment. Opinions vary as to the amount of the drug necessary for cure of gonorrhea, and figures ranging from 75,000 to 300,000 units¹⁷ have been given. It is probable that forty-eight hours

17. (a) Cohn, A.; Studdiford, W. E., and Grunstein, I.: Penicillin Treatment of Sulfonamide Resistant Gonococcal Infections in Female Patients, *J. A. M. A.* **124**:1124-1125 (April 15) 1944. (b) Lapenta, R. G.; Weckstein, A. M., and Sarnoff, H.: The Inadequacy of a Standardized Dosage of Penicillin in the Treatment of Gonococcal Urethritis, *ibid.* **128**:168-170 (May 19) 1945. (c) Harford, C. G.; Martin, S. P.; Hageman, P. O., and Wood, W. B., Jr.: Treatment of Staphylococcal, Pneumococcal, Gonococcal and Other Infections with Penicillin, *ibid.* **127**:325-329 (Feb. 10) 1945. (d) Greenblatt, R. B., and Street, A. R.: Penicillin for the Treatment of Chemoresistant Gonorrhea in the Female, *ibid.* **126**:161-163 (Sept. 16) 1944.

of therapy (320,000 units) is more than adequate for cure of the disease in the form under discussion. In speed and certainty of cure penicillin far surpasses any other agent ever used in treating gonorrhea.

REPORT OF CASES

CASE 1.—M. H., a 27 year old Negro woman who was living apart from her husband, was admitted to the Evans Memorial Hospital on Oct. 14, 1944, complaining of severe pain in the right upper abdominal quadrant, aggravated by respirations and of twenty-four hours' duration.

Past History.—Three years before the present illness, in November and December 1941, she had had pain, swelling and redness involving the left ankle, right foot and right elbow and, later, the dorsum of the right hand as well as the left shoulder. On Jan. 5, 1942, there was residual swelling over the left subacromial region, with tenderness and pain on motion of the left shoulder. There had been no symptoms indicative of gonococcic infection except a vaginal discharge. Gram-negative, intracellular diplococci were seen in the smear of materials from the cervix uteri. The sedimentation rate was 50.5 mm. per hour. The subacromial bursitis gradually improved following irrigation of the bursa and physical therapy. During the following eleven months she visited the clinic sporadically; in this period gonococci were cultured from the cervix several times. She was treated with local applications and with one course of sulfathiazole and was discharged as cured on Nov. 30, 1942, after three cultures and smears of cervical materials were negative for gonococci.

Present Illness.—Three months before entry she had fever, severe suprapubic pain, dysuria and a yellow vaginal discharge. These symptoms, except for a persistent discharge, subsided promptly after treatment with hot douches and rest in bed. Two weeks before admission (on the third day of her menstrual period) and one week after sexual exposure, the severe pain in the lower part of the abdomen returned, accompanied with malaise and anorexia. The symptoms continued until entry.

On the morning before entry the patient was awakened by a severe constant nonradiating pain in the right upper part of the abdomen, aggravated by deep breathing, coughing and motion of the trunk. No pains in the shoulders or back, chills, fever, nausea, vomiting or diarrhea was noted. There had been no previous similar attack. There had been no indigestion, intolerance to fatty foods or jaundice.

Physical Examination.—The patient was a well developed and well nourished young woman in moderate pain. The rectal temperature was 99.6 F. There was diminution of excursion of the right side of the diaphragm and slight dullness at the base of the right lung, but no other abnormalities of the lungs. The abdomen was slightly distended. There were pronounced tenderness and spasm over the right upper part of the abdomen and slight tenderness over the right lower quadrant and right lumbar region. The edge of the liver descended 2 cm. below the right costal margin on deep inspiration, which aggravated the pain. The spleen was not palpable. There was a profuse thick, creamy vaginal discharge. The uterine cervix was bilaterally lacerated, with extensive erosion. There were bilateral induration and thickening of the adnexa, more pronounced on the right. Motion of the cervix produced exquisite pain.

Laboratory Data.—Two Hinton tests of the blood elicited negative reactions. Results of several urinalyses were entirely normal. The white blood cell count on admission to the hospital was 11,300, with 87 per cent polymorphonuclear

leukocytes, and ranged between 10,000 and 13,000 until completion of treatment, when it dropped to normal. The icterus index and serum bilirubin content were normal. A roentgenogram of the chest showed a bilateral increase in hilar shadows, more pronounced on the right. A roentgenogram of the abdomen revealed only a moderately increased amount of gas in the colon. There were no radiopaque calculi. After completion of treatment an intravenous cholecystogram revealed entirely normal conditions. In smears of material from the urethra and cervix no intracellular gram-negative diplococci could be found. However, a heavy growth of gonococci was obtained from culture of the cervical secretions.

Course in the Hospital.—Because of lack of immediate confirmation of the diagnosis surgical consultation was obtained. The attending surgeon's diagnosis was acute cholecystitis, for which a prompt operation was strongly considered. However, symptomatic and conservative treatment was instituted until the report of the cultures was received. On the fourth day of hospitalization therapy with penicillin was begun, in doses of 20,000 units every three hours, intramuscularly. A total of 380,000 units was given. Within twenty-four hours after the institution of specific therapy all the abdominal pain had disappeared, and the course thereafter was one of rapid recovery. The rectal temperature, which had ranged between 98 and 101 F., rapidly subsided to normal after the beginning of treatment. The patient was discharged eleven days after admission. Cervical and urethral cultures made two and three weeks after discharge were negative for gonococci.

CASE 2.—M. G., a 30 year old white divorced waitress in a waterfront cafe, was admitted to the hospital on June 4, 1945, with a painful swelling of her right hand of three days' duration and pain over the entire right side of the abdomen and the top of the right shoulder of twenty-four hours' duration.

Past History.—At 15 years of age the patient had had septicemia and osteomyelitis, which had resulted in the formation of draining sinuses of the left humerus, left twelfth rib and lower end of the right tibia. After surgical drainage of these foci and removal of the rib she made a satisfactory recovery. Thirteen months before admission a diagnosis of gonorrhea was made on the basis of positive cultures at another hospital, to which she had been referred as a contact of a known patient. She was asymptomatic at that time. The serologic reaction of the blood was positive for syphilis, although she stated that she had not had symptoms of early infection. She was treated for two weeks with a sulfonamide compound and was told that the cultures were negative at the end of this period. During the next seven months several cultures of cervical and urethral materials were negative for gonococci. During the six months prior to admission she had received sporadic antisyphilitic treatment, consisting of six intramuscular injections of bismuth subsalicylate.

The patient's alcoholic intake was immoderate during the preceding seventeen years; it was particularly so during the last three, when she was intoxicated almost daily. She had separated from her husband four years earlier, after four years of marriage. She had had one abortion. Her husband was known to have had gonorrhea while she was living with him.

Present Illness.—Three days prior to admission the dorsum of her right hand was first noted to be painful. During the following forty-eight hours it became increasingly swollen, hot and red. One day before admission she was awakened by severe pain both in the right upper and lower quadrants of the abdomen and over the top of the right shoulder. The pain in the upper part of the abdomen did not radiate; it was constant, although made worse by coughing and deep breathing.

The pain on the top of the right shoulder radiated into the neck toward the ear; it was also exaggerated by coughing and deep inspiration but not by movement of the shoulder joint. On the morning of admission there was a slight ache in the left wrist but no other signs of inflammation. There were no chills, sweats or fever.

The menstrual flow was irregular during the three months before her illness, although it had previously been normal. Her last menstrual period was of fifteen days' duration, and it had ceased the day before the onset of her symptoms. The day before admission vaginal bleeding began again. She stated that she had never had leukorrhea, dysuria, urinary frequency or pyuria. The last sexual exposure had taken place four days before her symptoms began. There had been no other episodes of similar nature; she had never been jaundiced, nor had there been indigestion, intolerance to fatty foods or flatulence.

Physical Examination.—The patient was obese and acutely ill. The dorsum of the right hand was tender, hot, red and swollen, pitting on moderate pressure. Passive motion of the fingers was extremely painful, although motion of the wrist was unaffected. There was slight pain on movement of the left wrist, which appeared otherwise normal. The right shoulder joint was apparently normal; there was no tenderness, and motion in all directions was painless. The heart and lungs were normal. Diaphragmatic excursion was limited on the right because of pain. The abdomen was protuberant. There were decided spasm and tenderness over the entire right side of the abdomen. Pressure over the right upper quadrant accentuated the pain in the top of the right shoulder. There was a vague mass in the right upper quadrant which was considered by some observers to be an enlarged liver, although the lower edge was never palpated. No other masses were felt, and peristalsis was normal. Slight tenderness of the right costovertebral angle was noted. Pelvic examination showed a moderate amount of cervical erosion, with a transverse laceration. Movement of the cervix and palpation of both adnexa were exquisitely painful. No masses were felt. The urethra was normal. Skene's and Bartholin's glands were not palpable. There were several pulsating "spider" angiomas on the skin of the upper half of the body and many dilated venules on the face.

Laboratory Data.—Reaction of the blood to the Hinton test for syphilis was positive. Cultures of material from urethra and cervix were positive for gonococci, although smears were repeatedly found to be negative. The results of repeated urinalyses were normal. The white blood cell count was 23,400 with 76 per cent polymorphonuclear leukocytes on admission and gradually fell to 11,800 on discharge. The result of a complement fixation test for gonorrhea (Schwartz-McNeil) on the blood was positive. The total serum bilirubin was 1.14 mg. per hundred cubic centimeters, with 0.72 mg. per hundred cubic centimeters of direct reacting bilirubin on admission. There were 0.72 mg. and 0.18 mg. respectively, at the end of treatment. The cephalin flocculation reaction was negative. The sulfobromophthalein sodium excretion was within normal limits, as determined by the fractional method. A roentgenogram of the chest showed no abnormality except for elevation of the left side of the diaphragm.

Course in the Hospital.—As soon as the report of the cultures was known treatment with penicillin was started. The patient received 20,000 units intramuscularly every three hours. Within twenty-four hours after the institution of therapy, the temperature, which had previously ranged between 98 and 102 F. rectally, had returned to normal, and there was great improvement in her symptoms. After forty-eight hours of treatment there remained only slight residual soreness

in the right lower abdominal quadrant and moderate painless swelling of the dorsum of the right hand. Cultures of material from the urethra and cervix at this time were negative. Because she had not visited the syphilis clinic regularly, the patient was given a total of 1,200,000 units of penicillin in order to complete treatment of her latent syphilis. She left the hospital the fourteenth day after admission, entirely asymptomatic. Cultures after forty-eight hours of treatment and one and three days after the completion of treatment were negative.

CASE 3.—B. B., a 23 year old married Negro woman, was admitted to the surgical service of the Massachusetts Memorial Hospitals on Jan. 3, 1945, complaining of severe pain in the epigastrium of four hours' duration.

Past History.—In 1941 a diagnosis of early latent syphilis had been made. Since that time she had received antisyphilitic treatment consisting of a total of thirty-one injections of bismuthsubsalicylate in oil and thirty injections of various arsenical preparations.

Since 1940 she had had four pregnancies, the first an abortion at $4\frac{1}{2}$ months. The last child, born three months prior to this entry to the hospital, was apparently normal at birth but died at 7 weeks of age of unknown cause. There were two healthy children.

Present Illness.—During the six weeks prior to admission the patient had noticed a profuse purulent vaginal discharge and slight dysuria. Waves of nausea and anorexia occurred during the two days preceding entrance. On the night before admission she had a drenching sweat. She was awakened on the morning of admission by a severe pain in the upper part of the abdomen; the point of maximal intensity was in the midepigastrium. The pain was sharp and nonradiating and was made worse by coughing, talking or deep breathing. There was no vomiting. No shoulder ache or backache occurred. No increase in severity was produced by ingestion of food. There had been no similar episodes previously. No symptoms suggestive of disease of the gallbladder could be elicited.

Physical Examination.—The patient was thin, apprehensive and in evident pain. The heart was normal except for a rough grade II late systolic murmur, loudest over the second intercostal space at the sternal border on the left side. The murmur was not transmitted to the neck. The lungs were normal. In the abdomen pronounced tenderness and accompanying spasm of the musculature of the right upper quadrant and epigastrium were present. The liver was not palpable. Peristalsis was normal. Slight tenderness of the right costovertebral angle was found. Pelvic examination disclosed a thick purulent vaginal discharge, with erosion and laceration of the cervix. Only slight tenderness was elicited on palpation of either of the adnexa, and there were no masses.

Laboratory Data.—The Hinton test of the blood for syphilis elicited a positive reaction. The culture of cervical material was positive for gonococci, but the culture of urethral material was negative. The urine was normal except for a small amount of ketones. The white blood cell count was 15,800 with 92 per cent polymorphonuclear leukocytes on admission.

Course in the Hospital.—Treatment was immediately started with intramuscular injections of 15,000 units of penicillin, every three hours for a total of 195,000 units. The temperature, which was 102 F. on admission, had dropped to normal twelve hours later. At this time the patient was entirely asymptomatic. She left the hospital on the third day and failed to report for follow-up studies.

SUMMARY AND CONCLUSIONS

Three cases of gonococcic perihepatitis treated with penicillin are described in detail.

The clinical and pathologic picture of gonococcic peritonitis of the upper part of the abdomen is summarized as it has been developed since Stajano's original description.

From the data, the following conclusions may be drawn:

1. The disease occurs more commonly than is generally believed. It should be considered in the differential diagnosis for every young woman in whom an acute pain develops in the upper part of the abdomen, especially on the right side. It is most commonly misdiagnosed as acute cholecystitis.

2. Gonorrhea in the female is often latent and relatively asymptomatic; hence, it is difficult to diagnose clinically. The unreliability of smears is stressed; culture of the gonococcus is the only reliable method of diagnosis in many cases and should be carried out routinely.

3. The importance of correct diagnosis is obvious, since surgical intervention not only is unnecessary but may be actually harmful. Gonococcic peritonitis is easily and successfully treated with penicillin.

MYELOFIBROSIS, SPLENOMEGALY AND MEGAKARYOCYTIC MYELOSIS

Report of a Case

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FROM time to time cases have been reported in the literature in which there were splenomegaly and an unusual white blood cell count, which do not fit into any recognized pathologic category. Such cases are reported as: "Chronic nonleukemic myelosis"¹; "myelofibrosis associated with a leukemoid blood picture"²; "osteosclerosis with extensive extramedullary hematopoiesis and a leukemoid blood picture"³; "marrow sclerosis associated with massive myeloid splenomegaly"⁴; "splenomegaly with myeloid transformation"⁵; "megakaryocytic myelosis with osteosclerosis,"⁶ and "aleukemic myelosis with osteosclerosis."⁷ The similarity between these cases and the one reported

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here is striking and suggests the possibility of a disease entity which is infrequent enough to elude early recognition.

All of these cases in which there was splenomegaly have been characterized by megakaryocytes in the spleen, liver, lung, lymph nodes, peripheral blood and elsewhere with an accompanying disturbance in the number and type of circulating platelets. The circulating white blood cells, regardless of the total count, have shown myeloblastic forms. All of them have shown, either on roentgenologic studies or on autopsy, sclerosis or fibrosis of the bone marrow. The hemopoietic organs have shown not true leukemic infiltrations and proliferations but foci of extramedullary hemopoiesis. In addition, a strikingly large percentage have shown focal lesions in the lungs, liver or kidneys, variously described as infarcts, tubercles, abscesses or necrosis. In some of these cases acid-fast organisms have been demonstrated, although in a majority of the cases reported no studies have been carried out to determine the presence of such organisms.

In the present paper an additional case is reported, and its major features are correlated with the findings concerning similar cases in the literature.

REPORT OF A CASE

Clinical History.—The patient, a 36 year old white woman, was apparently well and healthy after the normal delivery of a 6 pound, 9 ounce (2,977 Gm.) baby girl on Oct. 11, 1944. Two days post partum an enlarged spleen was found. She was sent home from the hospital fourteen days after delivery but required continued medical care. A diagnosis of Banti's disease was made. She was readmitted to the hospital, and a splenectomy was done on Nov. 14, 1944. The pathologic report on the spleen indicated Hodgkin's disease. She left the hospital on Nov. 25, 1944, to convalesce under the care of relatives until March 1945, and during this time she gained approximately 35 pounds (16 Kg.). She then returned home and resumed care of her baby. In May 1945 her menstrual period came at the regular time but lasted twelve days, and she passed numerous large clots. At this time she caught a cold, and her temperature rose as high as 103 F. Her physician advised her to get more rest. Her general health failed to improve. She complained of weakness, night sweats, occasional headaches, a nonproductive cough and pleuritic pains localized at the level of the eighth thoracic vertebra. She was hospitalized for study on June 23, 1945. During this hospitalization she lost weight, and her stools became tarry.

Past History.—An appendectomy was performed in 1932. She had the usual diseases of childhood and had pneumonia in 1934. Her previous hospital record showed a single positive reaction to a Kahn test taken Oct. 15, 1944 (the reaction of blood from the cord at the time of delivery was reported negative), and she was considered syphilitic, being treated in 1943 and early 1944.

Family History.—Her mother died at the age of 42 from thyroid disease, her father died at the age of 79 from arteriosclerosis. One sister died of tuberculosis. Four other children in the family are living and well.

Physical Examination.—The temperature was 100.2 F., the pulse rate 100 and the respiration rate 24. The conjunctivas were pale. The lungs were clear, and

the examination of the heart revealed a soft systolic murmur at the base. There was a large, smooth, firm, mobile, nontender mass in the right upper and lower quadrants extending down to the rim of the pelvis. This was interpreted as an enlarged liver. The mass did not extend to the left side of the abdomen, which showed only the scar of the former splenectomy. The neurologic examination revealed no significant abnormalities. A moderate generalized nontender lymphadenopathy and a nonproductive cough were noted.

Special Studies.—The hemacytologic studies (table 1) revealed a progressive anemia with achromia, polychromatophilia, poikilocytosis and anisocytosis. The elevated white blood cell count and the presence of abnormal leukocytes were not apparent until the third admission. The most unusual findings were made during her fourth admission. The leukocyte count reached 115,000, then gradually declined to 34,000 with immature myeloid cells predominating. The platelet count extended well above 500,000, the platelets being too many to count in most instances. Many megakaryocytes in all stages of development and giant platelets were found in the peripheral blood smears (fig. 1).

The sternal marrow aspiration (table 2) was unusual in that the blood was under considerable pressure and clotted spontaneously in the syringe, so that the routine hematocrit determination was not done and good smears were difficult to obtain. The young myeloid cells predominated with a great increase in the number of megakaryocytes, and it was concluded that acute myeloid leukemia with pronounced megakaryocytic hyperplasia was indicated.

The serologic reports included two positive reactions to the Kahn test obtained prior to antisyphilitic therapy initiated in 1943, a single positive reaction to the Kahn test recorded during her first hospitalization in 1944, a negative reaction to the Kahn test of blood taken from the cord on delivery of her baby and two negative reactions to the Kahn test during the patient's last hospitalization. Studies of the spinal fluid were not done.

Studies of blood chemistry revealed a fasting glucose level of 80 mg., a cholesterol level of 236 mg. and a nonprotein nitrogen level of 33.5 mg. per hundred cubic centimeters, the latter being 55 mg. a few hours prior to death.

The results of urinalysis remained fairly constant, with an acid reaction, a specific gravity of 1.020, an albumin level of 35 mg. per hundred cubic centimeters and 7 to 9 leukocytes per high power field.

Additional laboratory studies revealed the following results: sedimentation rate, 6 mm. in five minutes and 32 mm. in sixty minutes; bleeding time, three and one-half minutes; clotting time, two minutes; coagulation time one minute; prothrombin time ranging between 57 and 92.3 per cent of normal, and blood type Rh negative.

Roentgenologic studies were not unusual prior to July 1945, at which time a pronounced enlargement of the liver was reported. A roentgenogram of the chest taken in August 1945 demonstrated significant widening of the upper mediastinum with some general cardiac enlargement. The left side of the diaphragm was completely obscured, and there was increased density of a moderate degree over both lower lung fields suggestive of minimal pleural effusion. A roentgenogram of the chest taken in September 1945, a few days prior to death, showed a significant diffuse flocculent increase in density involving both lung fields, most pronounced at the bases. However, the diaphragm leaves were well visualized and the angles clear. This suggested an acute pulmonary edema without pleural effusion.

TABLE 1.—*Blood Counts*

Date	R.B.C., Million	Hgb.	W.B.C.	My.	Juv.	Bands	Seg.	L.	B.	Promy.	Blasts	Stab	Trans.	Norm.	Mono.	Comment
First Admission																
10/19/44.....	3.8	56%	17,600	..	3	..	59	28	5	5	Achromia, polychro- matophilia
Second Admission																
11/13/44.....	3.5	58%	6,700	..	8	..	38	40	12	2	Anisocytosis, poly- chromatophilia, achromia
Third Admission																
6/21/45.....	2.0	31%	97,500	2	18	20	9	47	
6/30/45.....	1.9	30%	60,000	10	14	22	4	8	31	52	
Fourth Admission (Fig. 1)																
7/ 9/45.....	2.7	45% 6.5 Gm.	41,750	4	7	2	14	8	6	32	27	Platelets: 500,000; retic. 0.5%
7/12/45.....	2.4	46% 6.75 Gm.	34,350	4	2	5	8	7	5	10	59	{ There were many mega- karyocytes in all stages of development				Platelets: Innumerable
8/13/45.....	3.5	61% 8.7 Gm.	115,500	6	8	4	5	2	2	13	60	Platelets: Innumerable
9/18/45.....	1.9	36% 5 Gm.	35,000	8	11	7	4	5	6	22	37	Platelets: Innumerable

* These blood counts were selected as representative from daily counts during hospitalization.

Electrocardiographic studies resulted in no significant observations.

The basal metabolic rate, measured in July 1945, was + 15 per cent on the first test and + 20 per cent on the second test.

During the patient's last admission the pathologic material from the spleen was reexamined and reported suggestive of myelogenous leukemia.

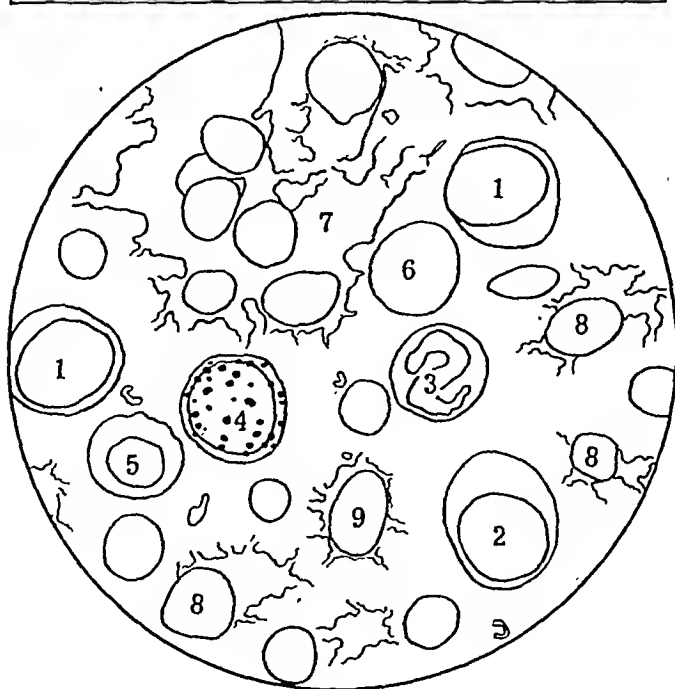


Fig. 1.—A composite drawing from blood smears obtained from the peripheral blood in the case herein reported: 1, myeloblast; 2, promyelocyte; 3, band neutrophil; 4, basophil; 5, normoblast; 6, macrocytic erythrocyte; 7, megakaryocyte; 8, detached portions of megakaryocytes, and 9, giant platelet.

Clinical Course.—The treatment was predominantly symptomatic with repeated blood transfusions of Rh negative blood. She grew progressively worse, becoming extremely emaciated and jaundiced and having increased malaise and discomfort. Her temperature was high because of sepsis, the peaks ranging between 104 F. and 105 F., with terminal evidence of delirium and mental changes. In the last week of her life ascites and jaundice were present. She died on Sept. 21, 1945.

Necropsy.—A necropsy was performed on Sept. 21, 1945.

General: The body was that of an extremely emaciated woman, 36 years of age and weighing approximately 98 pounds (44.5 Kg.). She had a sallow, jaundiced appearance. The right pupil was slightly smaller than the left, and both were dilated. There was an abdominal scar over the lower part of the right rectus muscle and a curved "hockey stick" scar covering the left side of the abdomen. A slight protuberance was noticeable about the umbilicus surrounded by an area of bluish discoloration beneath the skin which extended into the left upper quadrant. There was pitting edema over both ankles. There was a bed-sore about 2.5 cm. in diameter in the upper lumbar area. Generalized lymphadenopathy was prominent.

Thoracic Cavity: Both pleural cavities were obliterated by firm adhesions between the visceral and parietal pleurae. There was no free fluid in either pleural cavity. The lungs were removed with difficulty.

Lungs (fig. 2): The left lung weighed 720 Gm. It was subcrepitant, and the surface was studded with numerous small grayish white, firm nodules varying

TABLE 2.—*Bone Marrow*

July 9, 1945			
Myeloblasts.....	24.6	Lymphocytes.....	14.0
Promyelocytes.....	22.8	Monocytes.....	0.6
Myelocytes.....	6.2	Megaloblasts.....	0.4
Juvenile forms.....	4.8	Erythroblasts.....	0.2
Bands.....	6.6	Normoblasts.....	55.6
Segmented cells.....	13.8	Pronormoblasts.....	1.4
Eosinophils.....	0.8	Megakaryocytes.....	Great increase
Basophils.....	5.8		

in size from 0.1 to 0.5 cm. The larger vessels were patent; the bronchi contained a frothy material, and edema fluid could be expressed on compression of the lung tissue. The cut surface revealed massive studding of the tissue with small white nodules similar to those on the surface of the uncut organ, and free fluid ran from the cut surface. The lobes were equally involved. The right lung weighed 1,090 Gm. and was in all respects similar to the left lung. The hilar and mediastinal lymph nodes were enlarged and matted together and had a pinkish gray color when opened.

On microscopic study the alveolar septums were thickened, and their capillaries were crowded with red cells, occasional nucleated red cells, early myeloid cells, megakaryocytes and scattered fibrin. Some of the alveoli contained edema fluid; many contained cells of various types including heart failure cells. The bronchial epithelium showed areas of patchy erosion and the bronchi appeared empty. The surrounding connective tissue was edematous and infiltrated with round cells. Scattered throughout the sections were focal areas of infarction with early necrosis and degeneration of the lung tissue and deposition of considerable fibrin. The

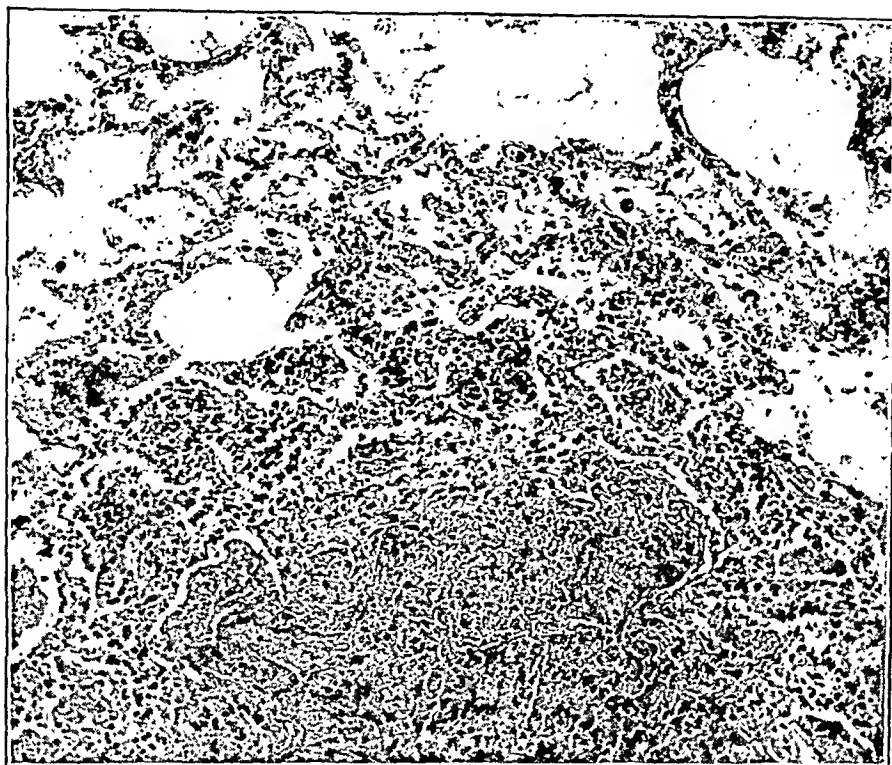


Fig. 2.—Photomicrograph of lung showing an area of focal infarction surrounded by a zone of extramedullary hemopoiesis.

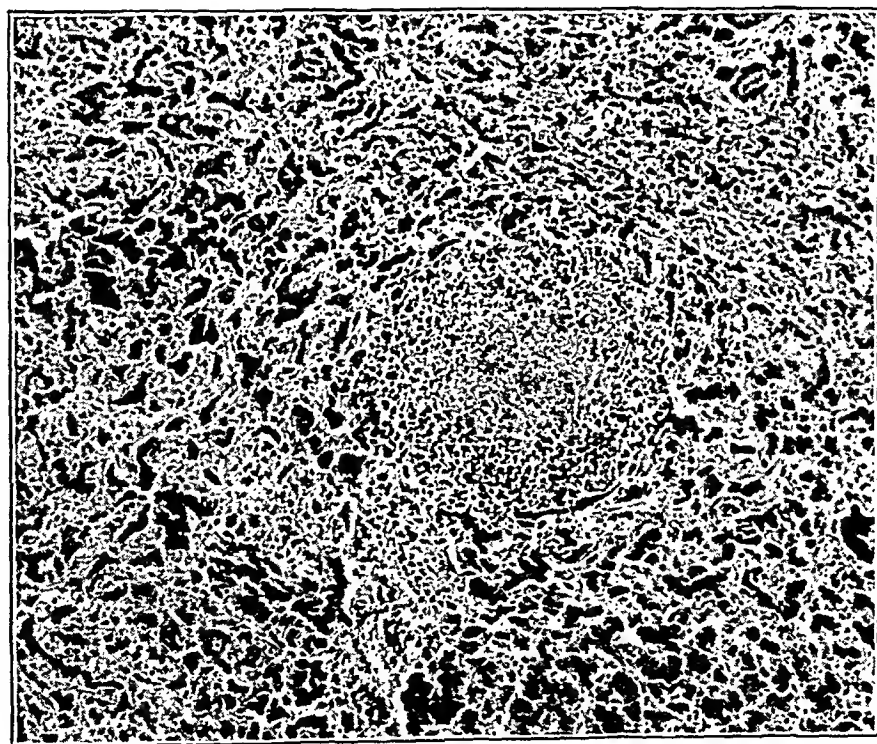


Fig. 3.—Photomicrograph of liver showing miliary tubercle and associated fibrosis.

infarcts were surrounded peripherally by a zone of cells, which include myeloblasts, megaloblasts, normoblasts, megakaryocytes and numerous phagocytes. This surrounding zone contained so many blast forms that it suggested extramedullary hemopoiesis. Epithelioid cells and lymphocytes were not seen. In sections stained by the Ziehl-Neelsen technic great numbers of acid-fast bacilli were found in the infarcted areas, and many were intracellular.

Heart: There was a small plaque on the pericardial surface of the heart over the left ventricle which measured approximately 0.9 cm. in diameter. The coronary ostia were patent. There were numerous subintimal plaques throughout the course of the coronary arteries, but the lumens remained widely patent. The heart valves, the auricles and the ventricles appeared normal.

The sections showed thinning of the myocardial bundles which were widely separated by edema. The coronary arteries showed subintimal thickening with early degenerative changes. An occasional early myeloid cell and phagocyte could be seen in the connective tissue surrounding the vessels.

Aorta: The aorta was normal in appearance, grossly and microscopically.

Abdominal Cavity: Five hundred cubic centimeters of dark, straw-colored fluid was found in the abdominal cavity. There was a small adhesion of the greater omentum to the scar on the lower part of the abdomen and to the stomach and transverse colon in the left upper quadrant. The omentum was almost completely devoid of fat. The peritoneal surfaces, both visceral and parietal, were studded with small grayish white nodules. The spleen and appendix were absent, having been surgically removed.

Liver (fig. 3): The liver weighed 2,670 Gm. Its lower border extended about 3 fingerbreadths below the right costal margin. The edge was broad and rounded. The surface was pale and studded with small grayish white nodules. The gallbladder contained 10 cc. of dark green bile. The cut surface of the liver was pale and slightly congested and showed an extensive peppering of the small grayish white nodules.

Histologic study showed areas of focal necrosis and infarction surrounded by zones of hemopoiesis similar to those seen in the lung. The hepatic cells and cords were small and surrounded by hyalinized connective tissue which obliterated many of the sinuses. The portal triad was similarly infiltrated with connective tissue and round cells. On and beneath the capsule were accumulations of immature erythrocytes and leukocytes. Special stains of these sections showed many acid-fast bacilli in the multiple necrotic zones, and many were intracellular.

Spleen (fig. 4): The spleen was surgically removed and not available for examination. Microscopic slides revealed considerable necrosis and scattered pigment. Numerous large myeloblasts and megaloblasts and frequent megakaryocytes were seen. The lymph follicles were few, and lymphocytes were sparsely distributed. The sinuses contained many myeloblasts, a few lymphocytes, red blood cells and much debris. An occasional multinucleate cell might be seen. Acid-fast stains of the tissue available failed to demonstrate the presence of organisms.

Gastrointestinal Tract: The gastrointestinal tract revealed nothing remarkable except for the nodules previously described on the peritoneal surface. The sections showed erosion of the superficial epithelium. The villi were infiltrated with round cells, many of which were lymphocytes and young myeloid cells. The muscular wall, particularly close to the serosal surface, showed focal areas of infarction surrounded by an accumulation of immature blood cells and occasional megakaryocytes.

Pancreas: The pancreas weighed 100 Gm. and was grossly normal. Microscopically, the acinar and islet cells were normal. There were considerable periductile and perivascular fibrosis and a thickened zone of periglandular fibrosis infiltrated by red cells.

Adrenal Glands: The adrenal glands appeared somewhat enlarged and firm, and the left was incorporated in the scar tissue adjacent to the previously removed spleen. The cut surface revealed thickening of the medulla and numerous tiny grayish white nodules.

The sections showed a thickened capsule. The cortical cells and cords were separated and replaced with connective tissue which was partially hyalinized. There were foci of necrosis surrounded by zones of hemopoiesis. The medullary

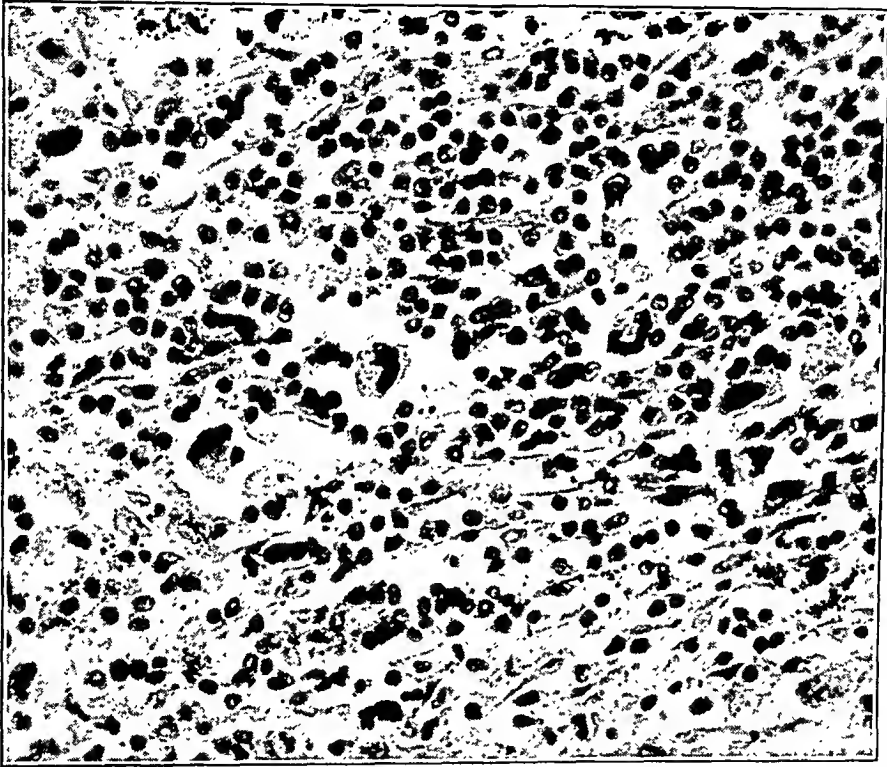


Fig. 4.—Photomicrograph of spleen. The sinuses are dilated and contain numerous megakaryocytes, many myeloblasts, a few lymphocytes, red blood cells and much debris.

zone was replaced by connective tissue, and only a few chromaffin cells remained. Scattered throughout the connective tissue were many large myeloblastic cells. The capillaries were distended, and there was hemorrhage into many of the necrotic foci. An occasional capillary was occluded by a thrombus. Numerous acid-fast bacilli were found in the necrotic areas.

Urinary Tract: The right kidney weighed 220 Gm. The external surface showed a slight lobulation. The cut surface revealed a cortex of normal thickness. The medullary zone was pale. The markings were somewhat indistinct. The pelvis was normal. The capsule stripped with ease. The left kidney weighed 215 Gm. and grossly was similar to the right, except for a single grayish white nodule measuring 4 mm. located in the upper pole. The ureters were normal.

The bladder appeared grossly normal except for the peritoneal surface previously described.

Microscopically the glomeruli and tubules showed many early degenerative changes, probably post mortem in character. There was considerable perivascular fibrosis. An infarct was found which showed caseation, necrosis and round cell infiltration. Huge numbers of acid-fast bacilli were demonstrated by special staining.

The surface of the bladder was covered with a thick fibrinocellular exudate containing large numbers of immature blood cells of all forms and occasional megakaryocytes. Some of these cells were found between the muscle bundles.

Genital Tract: The uterus, tubes and ovaries were covered with grayish white nodules on their peritoneal surfaces but were otherwise normal.

Breast: The breasts were normal.

Bone (fig. 5 and 6): The cortex of the ribs, sternum and vertebra was thickened and the trabeculae of cancellous portions were prominent. Firm white fibrous tissue obliterated the medullary spaces in the sectioned ribs. In the sternum and vertebra the medullary portion was filled with a uniform pinkish tissue.

The most pronounced change under the microscope was the extensive fibrosis which apparently had replaced the normal marrow. Scattered throughout the fibrous tissue were many megakaryocytes and myeloblasts and a few megaloblasts. Infarcted and necrotic zones which contained many acid-fast bacilli were found.

Lymph Nodes: The mediastinal, retroperitoneal and prevertebral lymph nodes were enlarged and matted together. The mesenteric nodes were slightly enlarged. All of these nodes cut with increased resistance and showed a uniform pink surface. Microscopic study of these lymph nodes recalled the findings in the sections prepared from the bone marrow. The resemblance to Hodgkin's disease under the low power was striking. There were pronounced fibrosis and an infiltration of myeloblasts, erythroblasts and megakaryocytes. Multinucleated cells resembling Sternberg-Reed cells were present. Some of the nodes were clearly necrotic, and the necrotic foci everywhere contained acid-fast bacilli.

Gallbladder: The gallbladder was apparently normal.

Brain: Gross and microscopic examinations of the brain revealed extensive congestion. No nodules similar to those previously described were found.

Pathologic Diagnosis: The pathologic diagnosis was of myelofibrosis, splenomegaly and megakaryocytic myelosis and miliary tuberculosis.

Anatomic Findings: Hemopoietic organs. There were myelofibrosis, extramedullary hemopoiesis and a leukemoid reaction with megakaryocytosis. The spleen had been removed surgically, the lymph nodes were enlarged, the liver was enlarged with fibrosis and there was miliary tuberculosis.

COMMENT

The essential observations in this case were: (1) an apparently well and normal 36 year old woman previous to her delivery on Oct. 11, 1944; (2) a chronic progressive illness associated with splenomegaly discovered immediately post partum; (3) appearance of a typical myelogenous leukemia with megakaryocytosis; (4) observation at necropsy of myelofibrosis, extramedullary hemopoiesis and atypical miliary tubercles massively infested with acid-fast, gram-positive bacilli, and (5) absence of typical leukemic infiltrations.

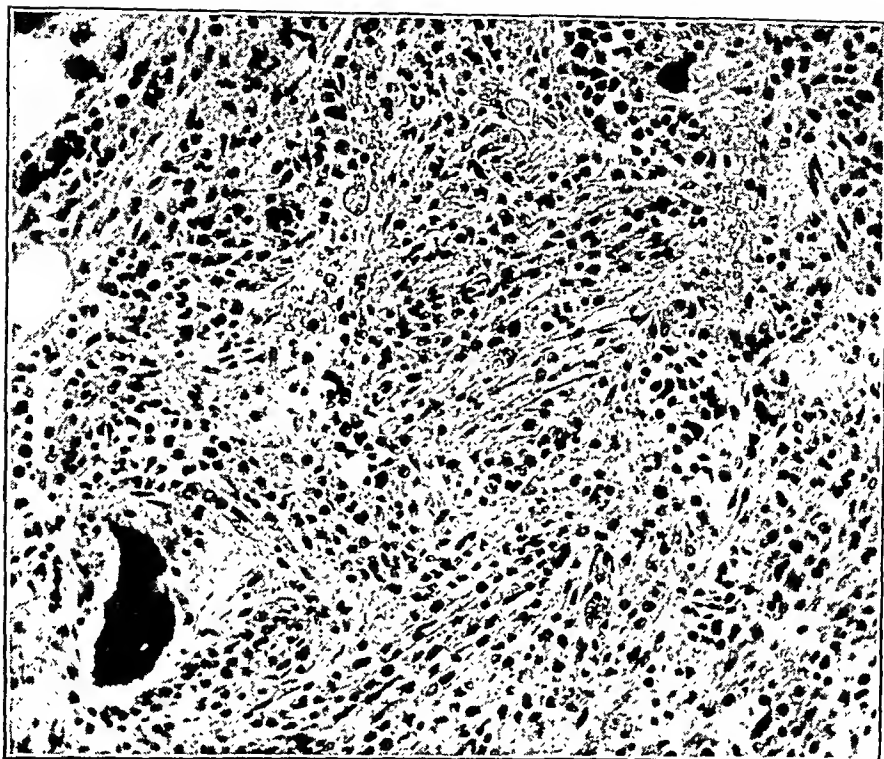


Fig. 5.—Photomicrograph showing extensive myelofibrosis seen in the vertebra.

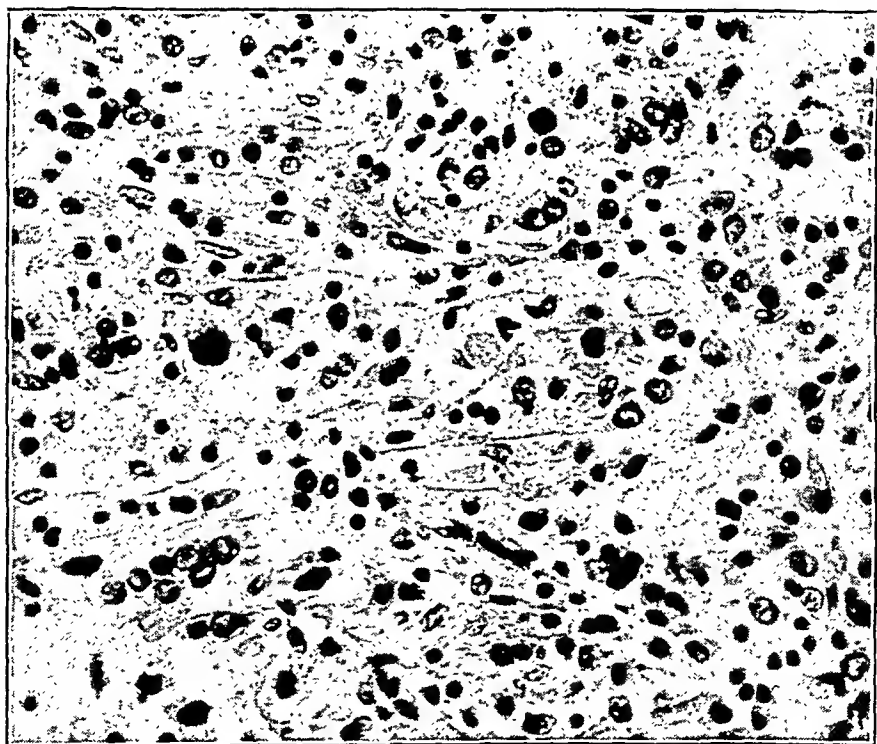


Fig. 6.—Higher magnification of the bone marrow in figure 5. Fibrous tissue replaces most of the normal myeloid elements.

The clinical course was interpreted as an unusually acute phase of myelogenous leukemia presenting the added complication of possible embolism and infarction because of the extremely high platelet count. The presence of tuberculosis was not considered likely. Even at necropsy the multitude of tiny, grayish white nodules did not resemble tubercles but rather leukemic nodules. Only after microscopic examination, when the nodules were found not to be leukemic, was the possibility of tuberculosis considered.

Carpenter and Flory^{1b} reported a case of splenomegaly with a leukemic blood picture similar in every detail to the case presented here. They described the firm, grayish nodules in the lung filled with acid-fast bacilli and bone marrow lesions microscopically similar. They attributed the miliary tubercles to a coincidental terminal miliary tuberculosis. In their case 1 Churg and Wachstein⁸ described pinhead-sized abscesses in the lung and liver. These abscesses were surrounded by a collection of myeloid cells. In their case 3 similar lesions were seen. The lungs in this case presented healed primary tuberculosis with calcified lymph nodes and no leukemic infiltrations. No interpretation was offered in these cases for the abscesses nor was the presence of an organism or its type determined. Similarly, Taylor and Smith⁴ reported a patient with pronounced foci of necrosis in the liver, and in some of these areas formation of young fibrous tissue was demonstrated. Here again there was no interpretation of the necrotic foci. Heinle and Weir,⁹ on the other hand, reported a case of "morphologic obliteration of chronic myeloid leukemia by active tuberculosis." At autopsy leukemic infiltrations of the various organs as encountered in true leukemia were not observed. Acid-fast organisms were found but were not further identified by culture or other means. Krasso and Nothnagel¹⁰ reported generalized miliary lesions resembling anemic infarcts and filled with many acid-fast organisms in a case believed to be of myelogenous leukemia. The character of these organisms was disputed by subsequent investigators. Klemperer¹¹ stated, "In myeloid leucemia with predominance of megakaryocytes within the spleen, I have seen the giant cells in conspicuous abundance at the periphery of anemic infarcts."

8. Churg, J., and Wachstein, M.: Osteosclerosis, Myelofibrosis and Leukemia, *Am. J. M. Sc.* **207**:141, 1944.

9. Heinle, R. W., and Weir, D. R.: Morphologic Obliteration of Chronic Myeloid Leukemia by Active Tuberculosis: Report of a Case, *Am. J. M. Sc.* **207**:450, 1944.

10. Krasso, H., and Nothnagel, H.: Atypische Tuberkulose (Geflügeltuberkulose?) bei myeloischer Leukämie, *Wien. Arch. f. inn. Med.* **11**:507, 1925.

11. Klemperer, P., in Downey, H.: *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 1651.

This is the same pathologic picture seen in miliary lesions in the case presented here.

Flory and Carpenter,¹¹ in reviewing a series of cases of this type, pointed out their similarity and concluded that the syndrome of non-leukemic myelosis may be due to "chronic progressive hyperplasia of multipotential mesenchymal tissues caused by an unknown stimulus." The observations in the case reported here suggest that this unknown stimulus could be the acid-fast organisms found in such huge numbers in the miliary lesions. Further studies, unfortunately, were not undertaken at the time of necropsy to identify the exact nature of these acid-fast organisms.

Judging from other case reports in the literature and careful pathologic studies by such workers as L'Esperance and Branch, it is possible that these cases represent the result of human infestation by avian tuberculosis. If the lesions in this case represent tubercles, they are highly atypical and pathologically suggest lesions found experimentally in avian tuberculosis. L'Esperance¹² devoted considerable time and energy to the pathogenicity of avian tuberculosis and its possible relationship to Hodgkin's disease. Branch¹³ reviewed much of her work and the literature on the avian tubercle bacillus, concluding that it can infect man. Löwenstein¹⁴ quoted reports on 4 cases of myelogenous leukemia from which avian tubercle bacilli were recovered. Krasso and Nothnagel¹⁰ stated their belief that the acid-fast bacillus in their case was avian tuberculosis. Branch¹³ pointed out the following characteristics of avian tuberculosis from his review of the literature: (1) there is a long-continued remittent fever with elevation of the temperature in the evening; (2) a splenic tumor is almost always present; (3) the liver is frequently enlarged; (4) the bone marrow, kidneys, lymph nodes and skin are frequent sites of involvement; (5) the lungs have multiple grayish nodular foci; (6) there is a complete absence of proliferative changes and caseation, and (7) there are large numbers of tubercle bacilli (predominantly intracellular) in the focal lesions.

12. L'Esperance, E. S.: Experimental Innoculation of Chickens with Hodgkin's Nodes, *J. Immunol.* **16**:37, 1929; Pathogenicity of Avian Tubercle Bacillus, *ibid.* **16**:27, 1929; Study of Case of Hodgkin's Disease in Child, *ibid.* **18**:127, 1930.

13. Branch, A.: Avian Tubercle Bacillus Infection with Special Reference to Mammals and to Man: Its Reported Association with Hodgkin's Disease, *Arch. Path.* **12**:253 (Aug.) 1931.

14. Löwenstein, E.: Ueber Septikämie bei Tuberkulose, *Ztschr. f. Tuberk. u. Heilstättenw.* **7**:491, 1905; Ueber das Vorkommen von Geflügel-Tuberkulose beim Menschen, *Wien. klin. Wchnschr.* **26**:785, 1913; Das Krankheitsbild der Hühnertuberkulose beim Menschen, *Ztschr. f. Tuberk.* **41**:18, 1924; Das Krankheitsbild der Hühnertuberkulose beim Menschen, *Med. Klin.* **24**:1782, 1928.

It is possible that acid-fast organisms other than forms of tuberculosis may give rise to characteristic infections in man. Among these are the various actinomycoses. Cobbett¹⁵ cultured acid-fast organisms of an undetermined variety from lesions on a soldier in 1918.

It is not the purpose of this paper to propose the origin of this syndrome or to affirm that it is a form of tuberculosis, but rather to bring this possibility to the attention of others and to encourage a definite search for this etiologic factor in subsequent cases.

SUMMARY

Numerous cases of splenomegaly presenting the same clinical and pathologic features but bearing a variety of titles and interpretations are reported in the literature.

A report is given of a case of splenomegaly, hepatomegaly, a leukemoid blood picture, megakaryocytosis, extramedullary hematopoiesis, myelosclerosis and atypical miliary tuberculosis.

It is suggested that the entire syndrome may be due to the acid-fast organism seen in the miliary lesion which pathologically resembles avian tuberculosis.

Captain Otis Wildman (MC) U.S.N. and Commander C. F. Geschickter (MC) U.S.N.R. assisted in the pathologic study of this case. The photographs were made by Lieutenant (jg) J. R. Borland (HC) U.S.N.R. The clinical material was furnished by Lieutenant Commander G. R. Lamb (MC) U.S.N.R.

710 Lake Shore Drive, Chicago, Ill.

15. Cobbett, L.: An Acid Fast Bacillus Obtained from a Pustular Eruption, Brit. M. J. 2:158, 1918.

EFFECT OF ATROPINE ON THE BRANHAM SIGN IN ARTERIOVENOUS FISTULA

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AND

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THE BRANHAM¹ sign is of proved value in the diagnosis of arteriovenous fistulas. It consists of a slowing of the pulse rate on temporary obliteration of the fistula. The response to obliteration is prompt, occurring within seconds, suggesting a reflex arc with the vagus nerve as the efferent limb. It would seem possible, therefore, to eliminate the Branham phenomenon in patients with arteriovenous fistulas by paralysis of the vagus nerve induced by atropine. This has been attempted previously with variable results.² In the light of our experiences, this variability appears related only to the degree of completeness of the atropine effect attained.

PROCEDURE

The subjects were soldiers who had sustained wounds which led to the development of arteriovenous fistulas. A solution of atropine sulfate in distilled water was administered intravenously. The doses varied from 1.7 to 1.95 mg. of the drug. In an earlier case, the administration of three successive doses of 0.065 mg. of atropine sulfate failed to induce as striking an effect as did the single administration of the entire dose. In this study the latter procedure was employed in all except case 9, in which initial tachycardia warranted caution.

Observations were made on heart rate, pupillary changes and dryness of the mouth as evidence of atropinization. The changes in heart rate and pupillary size usually appeared within three minutes. The dryness of the mouth was slower in development. The subject was recumbent during the period of observation and had rested for fifteen to thirty minutes before basal studies were made. The heart rate was counted for a full minute with the stethoscope, and the blood pressure was determined by the use of a mercury manometer with check readings. Manual obliteration of the fistula was judged complete on disappearance

From the Vascular Surgery Center, Ashford General Hospital.

1. Branham, H. H.: Aneurismal Varix of the Femoral Artery and Vein Following a Gunshot Wound, *Internat. J. Surg.* **3**:250, 1890.

2. (a) Lewis, T., and Drury, A. N.: Observations Relating to Arteriovenous Aneurism, *Heart* **10**:301, 1923. (b) Elkin, D. C.: Arteriovenous Aneurysm, *J. M. A. Georgia* **25**:417, 1936.

of the bruit at the site of the fistula. None of the subjects had a sensitive carotid sinus mechanism.

As is seen in the accompanying chart, there was a considerable fall in the pulse rate on obliteration of the fistula prior to atropinization.

CASE & DIAGNOSIS	CONTROL		DURING OBLIT. OF FISTULA		EFFECT OF ATROPINE		TIME IN MINUTES AFTER INJECTION					
	PULSE	B.P.	PULSE	B.P.	DOSE & REACTION							
						3	5	8	11	15		
No. 1 Arteriovenous Fistula Popliteal Vessels	74	135/66	56	130/84	1.95 mg. wide pupils no oral dryness	128	132	132	128	120	Pulse Control	
						170/100	158/106	150/100	148/98	144/96	B.P.	
						120	128	122	124	120	Pulse During Oblit	
						170/114	170/114	150/110	154/108	144/110	B.P.	
						120	120	120	122	120	Pulse Control	
						136/94	136/94	132/94	130/90	126/90	B.P.	
No. 2 Arteriovenous. Fistula Popliteal Vessels	84	118/74	62	120/88	1.95 mg. wide pupils dryness ++	120	120	120	122	120	Pulse Control	
						136/104	132/94	134/98	130/96	130/96	B.P.	
						120	120	120	120	118	Pulse During Oblit.	
						136/104	132/94	134/98	130/96	130/96	B.P.	
						118	118	116	114	118	Pulse Control	
						150/90	140/90	142/90	145/98	134/90	B.P.	
No. 3 Arteriovenous Fistula Axillary Vessels	72	150/74	64	156/90	1.95 mg. wide pupils dryness +++	110	112	108	112	108	Pulse Control	
						158/108	150/110	156/110	150/110	150/110	B.P.	
						124	120	124	124	126	Pulse During Oblit	
						150/80	140/80	144/76	134/76	140/76	B.P.	
						124	120	124	124	122	Pulse Control	
						180/110	178/112	178/116	170/120	166/114	B.P.	
No. 4 Arteriovenous Fistula Femoral Vessels	80	124/60	62	140/84	1.95 mg. wide pupils dryness +	124	120	124	124	122	Pulse Control	
						180/110	178/112	178/116	170/120	166/114	B.P.	
						110	110	108	106		Pulse During Oblit	
						140/70	134/70	130/68	130/70		B.P.	
						106	108	104	104		Pulse Control	
						140/70	138/82	138/80	136/80		B.P.	
No. 5 Arteriovenous Fistula Brachial Vessels	72	124/56	60	124/68	1.95 mg. Very wide pupils dryness +++	106	108	104	104		Pulse During Oblit	
						140/70	138/82	138/80	136/80		B.P.	
						136	130	122	128		Pulse Control	
						110/68	110/70	110/70	108/68		B.P.	
						128	130	120	124		Pulse During Oblit	
						112/74	114/80	114/75	112/74		B.P.	
No. 6 Arteriovenous Fist. Common Carotid Artery; Int. Jugular Vein.	98	122/60	84	122/70	1.95 mg. wide pupils dryness ++	128	124	120	120		Pulse Control	
						118/60	106/60	108/60	110/60		B.P.	
						120	120	118	116		Pulse During Oblit.	
						122/80	124/80	120/80	120/80		B.P.	
						112	110	120	110		Pulse Control	
						120/70	118/74	110/72	110/70		B.P.	
No. 7 Arteriovenous Fistula Femoral Vessels	78	116/66	60	120/70	1.95 mg. wide pupils dryness ±	108	110	110	106		Pulse During Oblit	
						124/90	120/90	122/90	116/92		B.P.	
						176	180	160	156		Pulse Control	
						120/74	124/76	120/78	118/60		B.P.	
						178	178	168	160		Pulse During Oblit	
						124/88	122/90	116/90	118/90		B.P.	
No. 8 Arteriovenous Fistula Femoral Vessels	140	140/76	120	134/90	1.0 mg. wide pupils dryness ++	80		78	102		Pulse Control	
						120/78		118/80	116/80		B.P.	
						72		84	98		Pulse During Oblit	
						130/88		118/90	116/90		B.P.	

Results of atropinization studies; the symbols +++, ++, + and ± represent decreasing degrees of oral dryness.

This is listed as the control reading. There is likewise shown the failure to obtain this fall in the pulse rate after atropinization except in case 10.

Of correlated interest were the associated changes in blood pressure following obliteration of the fistula prior to atropinization. Usually the

PRECORDIAL LEADS IN CHILDREN

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IN 1935 Master, Dack and Jaffe¹ carried out the first investigation on precordial leads in 72 healthy children. They recorded seven precordial leads each separated by a distance of 2 cm. at the level of the fourth intercostal space, beginning at the left margin of the sternum, and found that the T wave, initially negative, became positive in the proximities of the apex.

A year later Rosenblum and Sampson² recorded in 15 children the chest-back lead and three precordial leads in the second, third and fourth intercostal space at the left margin of the sternum. Contrary to what was shown by their controls (66 records on adults without cardiac lesions in which the T wave was negative), this wave was found to be positive in the precordial leads in 64 per cent of the children, diphasic or isoelectric in 32 per cent and negative in only 4 per cent.

Among 50 normal children Moia³ found the T wave positive in 56 per cent.

Robinow, Katz and Bohning (1936),⁴ recording a single precordial lead in the fourth intercostal space at the left margin of the sternum, found that the T wave was positive in 58 per cent of 61 children of different ages. They arrived at the conclusion that the younger the children the greater the percentage of positive T waves and that at about the age of 14 the precordial electrocardiogram becomes similar to that of the normal adult.

From the National Academy of Medicine, Institute of Physical Research Applied to Human Pathology, Cardiological Section, Prospero Baurin Foundation.

1. Master, A. M.; Dack, S., and Jaffe, H. L.: Chest Leads in Normal Children, *Proc. Soc. Exper. Biol. & Med.* **32**:1529, 1935.

2. Rosenblum, H., and Sampson, J. J.: A Study of Lead IV of the Electrocardiogram in Children with Especial Reference to the Direction of Excursion of the T Wave, *Am. Heart J.* **11**:49, 1936.

3. Moia, B.: La IV derivación o derivación torácica en 50 niños normales, *Rev. argent. de cardiología* **2**:26, 1935.

4. Robinow, M.; Katz, L. N., and Bohning A.: The Appearance of the T-Wave in Lead IV in Normal Children and in Children with Rheumatic Heart Disease, *Am. Heart J.* **12**: 88, 1936.

In 1937 Master, Dack and Jaffé⁵ studied the precordial leads in 71 children between the ages of 2 and 15 years. They recorded the electrocardiogram from seven points of the precordial region from the right margin of the sternum to the left, placing the electrodes, separated by a distance of 2 cm., in the fourth intercostal space in children under 6 and in the fifth intercostal space in children over 6 years of age. They employed the CF lead. Their results proved: frequent absence of the P wave; P-R interval from 0.1 to 0.14 second; Q of greater voltage and R of less amplitude in points 4, 5, 6 and 7; QRS duration between 0.06 and 0.08 second; R-T with deviations of 1 mm.; T positive and diphasic in 60 per cent of cases in points 4, 5, 6 and 7. They observed also modifications of Q, R and T waves due to respiration and changes of position of the body. In children of 14 to 15 years of age the appearance of the precordial electrocardiogram resembles that of the adult (negative T waves). These authors claim that the positive T wave is a characteristic of the precordial electrocardiogram in children, but due to the fact that either positive or negative T waves may be found, they do not give diagnostic value to the configuration of T. They found no relation between the positivity of T, the electrical axis and the roentgenologic image of the heart.

In all the investigations mentioned in the foregoing paragraphs the precordial leads were taken in such a way that the relative positivity of the precordial electrode is represented by a downward deflection (\mp).

Using the modern standardized technic (the relative positivity of the precordial electrode being recorded by an upward deflection (\pm), Master⁶ believes that the negative T waves are of normal occurrence in the precordial leads of children. Latorre (1941)⁷ and Seham and Moss (1942)⁸ do not find any clinical value in the precordial lead in children.

MATERIAL

Our work was carried out on 50 healthy children of the Preventorio Rocca, who were divided into three groups: A (0-2 years old), 13 children; B (3-5 years), 16, and C (6-10 years), 21.

5. Master, A. M.; Dack, S., and Jaffé, H. L.: The Precordial Lead of the Electrocardiogram of Normal Children, *Am. J. Dis. Child.* **53**:1000 (April) 1937.

6. Master, A. M.: The Electrocardiogram and X-Ray Configuration, of the Heart, ed. 2, Philadelphia, Lea & Febiger, 1942, figs. 14B, 14C, 28 and 28B.

7. Latorre, B.: Desarrollo y evolución del electrocardiograma en el lactante normal y prematuro sano, en su primer año de vida, *Rev. chilena de pediat.* **12**:627, 1941.

8. Seham, M., and Moss, A. J.: Electrocardiography in Pediatrics, *Arch. Pediat.* **59**:419 (July); 525 (Aug.) 1942.

TABLE. 1.—*Amplitude of Ventricular Deflections in Standard and Precordial Leads*

	D ₁	D ₂	D ₃	V ₁	V ₂	V ₃	V ₄	V ₅	V ₆
Group A, 0-2 years									
Q wave									
Minimum.....	0	0	0	0	0	0	0	0	0
Maximum.....	2	3	4	0	0	0	1	6	3
Medium.....	0.7	1.3	1.6	0	0	0	0.09	0.8	1.05
R wave									
Minimum.....	0	0	1	7	7	9	9	8	1
Maximum.....	10	14	11	20	22	17	18	25	15
Medium.....	4.2	5.7	5.6	12	12	11	11	13	8.3
S wave									
Minimum.....	0	0	0	0	3	5	4	2.5	1.5
Maximum.....	7	5	3.5	16	15	10	13	12	10
Medium.....	3.9	2.7	1.1	6.3	6.4	7.7	8.4	6.6	4
T wave									
Minimum.....	0.5	1	0	0.5	0.5	1	0.5	0.5	1
Maximum.....	5	4	3	6	4.5	4.5	4	6	6
Medium.....	2.6	2.4	0.2	2.1	1.2	0.2	0.4	2.1	2.3
R-S or QSR waves									
Minimum.....	5	2.5	3	7	13	16	17	5.5	3
Maximum.....	17	16	11	36	32	24	30	31	21
Medium.....	8.1	8.4	6.7	20	20.2	10.5	20.2	19.3	2.09
Group B, 3-5 years									
Q wave									
Minimum.....	0	0	0	0	0	0	0	0	0
Maximum.....	1	2	3	0	0	0	2.5	3	2.5
Medium.....	0.1	0.3	1.4	0	0	0	0.3	0.8	0.7
R wave									
Minimum.....	2	3	2	2	5	5	5	7.5	5
Maximum.....	10	12	10	9	16	20	22	22.5	18.7
Medium.....	5	7.6	5.6	5.5	9.5	11	13	14	9.1
S wave									
Minimum.....	0	0	0	2.5	5	3	3	0	0
Maximum.....	6	4	5	15	22.5	21	18	10	5
Medium.....	2.5	1.6	0.8	7.1	12	11	10	5.5	2.2
T wave									
Minimum.....	0	0.5	0	0.5	0.5	0.5	0.5	2	1
Maximum.....	4	4	1.5	4	4	7.5	8.5	6	6
Medium.....	1.7	1.8	0.2	1.9	0.4	1.9	1.9	2.7	2.2
R-S or QSR waves									
Minimum.....	3	4	2	5	15	8	10	8	5
Maximum.....	15	12.5	12	24	37.5	34.5	33.7	28	23.7
Medium.....	7.6	9.1	6.5	12.6	22.9	23.7	23.9	19.2	10.7
Group C, 6-10 years									
Q wave									
Minimum.....	0	0	0	0	0	0	0	0	0
Maximum.....	2	3	3	0	0	1	1.5	4	3
Medium.....	0.2	0.5	0.6	0	0	0.4	0.2	0.6	0.4
R wave									
Minimum.....	2	3	0.5	1	2	4	5	5	3
Maximum.....	9	13	13	8	14	18	17	17	12
Medium.....	5	7.2	4.2	4	7.4	10	11	9.9	7.1
S wave									
Minimum.....	0	0	0	1	3	3	1	0.5	0
Maximum.....	3	3.5	4	15	17.5	17.5	21	13	5
Medium.....	1.6	1.4	0.7	7.4	8.9	9.5	7.6	4.1	1.8
T wave									
Minimum.....	0.5	0.5	0	0.5	0.5	0.5	0.5	0.5	0.5
Maximum.....	4	5	1	2.5	3	5	5	4.5	4
Medium.....	2	2.1	0.1	1	0.1	1.6	2.3	2.3	1.7
R-S or QSR waves									
Minimum.....	3	5	2	2	8	11	10	5.5	4
Maximum.....	13	13	13	18.5	31	28.5	32.2	28.5	14
Medium.....	6.6	8.7	5	11.4	17.6	19.7	19	14	8.9

TECHNIC

Besides the "standard" leads (I, II and III) six precordial leads were recorded following the specifications of the Committee of the American Heart Association. The Wilson terminal electrode was used (V_1 , V_2 , V_3 , V_4 , V_5 and V_6) as well as the unipolar limb leads (V_R , V_L and V_F).

RESULTS

Table 1 shows the measurements of the different waves recorded in the mentioned leads for the three groups of ages, and table 2 a comparison of these values with those of adults. We shall make special

TABLE 2.—*Mean Voltage of the Different Waves in Multiple Precordial Leads in Children and Adults*

	Wave				
	Q	R	S	T	R-S
V_1 0-2 years.....	0	12	6.3	2.1	20
3-5 years.....	0	5.5	7.1	1.9	12.6
6-10 years.....	0	4	7.3	1	11.4
Adults.....	0	4.16	11.05	1.23	15.21
V_2 0-2 years.....	0	12	6.4	1.2	20.2
3-5 years.....	0	9.5	12	0.4	22.9
6-10 years.....	0	7.4	8.9	1.1	17.6
Adults.....	0	9.05	16.23	6.22	25.27
V_3 0-2 years.....	0	11	7.7	0.2	18.7
3-5 years.....	0	11	11	1.9	23.7
6-10 years.....	0.4	10	9.5	1.6	19.7
Adults.....	0.013	16.70	9.05	6.26	25.75
V_4 0-2 years.....	0.09	11	8.4	0.4	20.2
3-5 years.....	0.3	13	10	1.9	23.9
6-10 years.....	0.2	11	7.6	2.3	19
Adults.....	0.37	22.31	5.32	5.66	27.63
V_5 0-2 years.....	0.8	13	6.6	2.1	19.3
3-5 years.....	0.8	14	5.5	2.7	19.2
6-10 years.....	0.6	9.9	4.1	2.3	14
Adults.....	0.57	18.78	1.93	4.59	20.70
V_6 0-2 years.....	1.05	8.3	4	2.3	12.3
3-5 years.....	0.7	9.1	2.2	2.2	10.7
6-10 years.....	0.4	7.1	1.8	1.7	8.9
Adults.....	..	5.81	6.09	2.55	11.91

The values for adults have been taken from "Nomenclature and Criteria for Diagnosis of Diseases of the Heart," 1939.

reference in this paper to the precordial leads (V_1 , V_2 , V_3 , V_4 , V_5 and V_6), which showed the following principal characteristics:

Group A (0 to 2 Years).—The electrocardiographic peculiarities of this group were:

(1) Absence of the Q wave up to V_3 .

(2) R wave of great amplitude, larger than S in most cases in V_1 (fig. 1). The maximum height obtained in V_1 was 20 mm. and its average value 12 mm. These figures persist without great variations up to V_5 and decrease in V_6 to a middle value of 8.3 mm.

(3) S wave of a relatively small amplitude in V_1 . It increases gradually up to V_4 and decreases in V_5 and V_6 (fig. 2). Certain equilibrium or diphasism R-S may be observed in some cases in the right precordial leads (fig. 3).

(4) T wave frequently negative or diphasic (\mp) in the first three leads (in V_1 90 per cent, V_2 85 per cent and V_3 55 per cent), then less

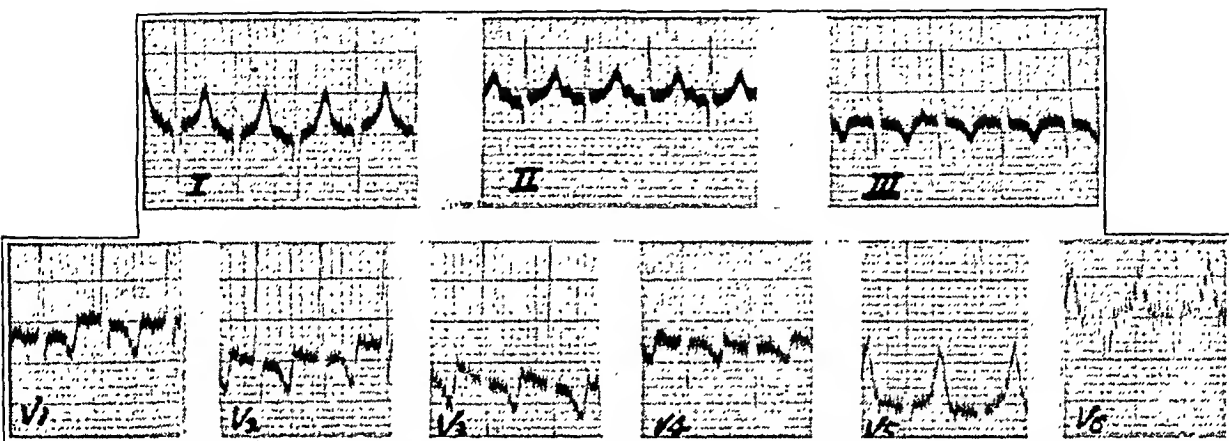


Fig. 1.—Electrocardiogram of a 33 day old child. The R wave has great amplitude in V_1 . The T wave is negative in V_1 , V_2 , V_3 and V_4 .

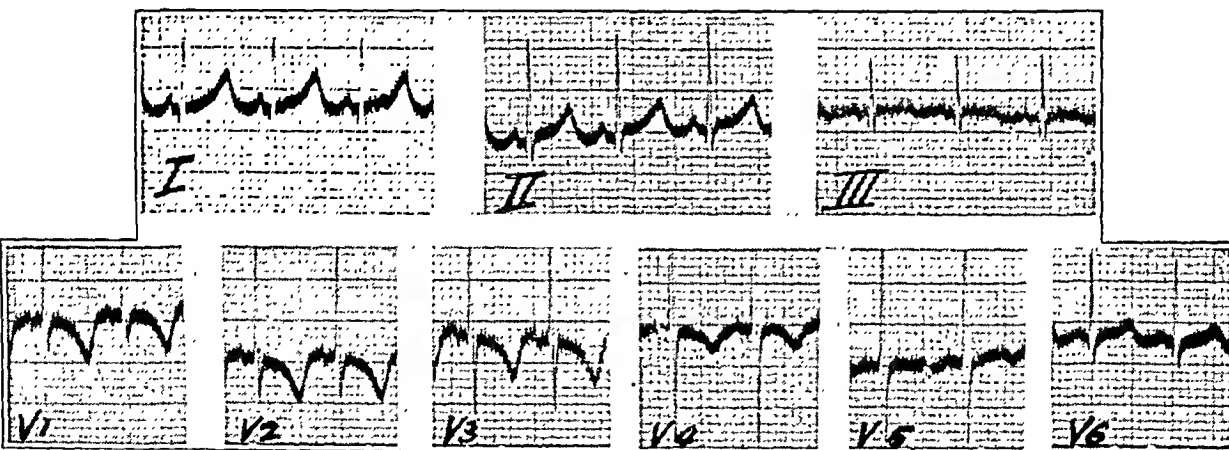


Fig. 2.—Electrocardiogram of a 70 day old child. The S wave is of small amplitude in V_1 . The T wave is negative in V_1 , V_2 , V_3 , V_4 and V_5 .

frequently negative in the points to the left, although the negativity or diphasism persisted frequently (20 per cent of cases) even to V_6 (fig. 4). The negativity or diphasism of T is sometimes decided. Generally the obliqueness of the descendant branch is greater than that of the ascendant one, and the junction of both branches under the isoelectric level is the vertex of an acute angle.

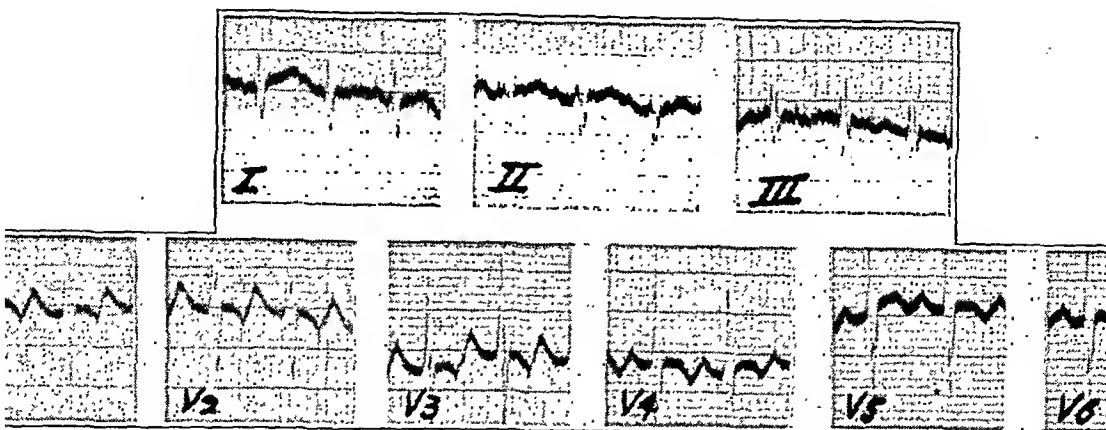


Fig. 3.—Electrocardiogram of a 30 day old child. The R and S waves are of nearly equal voltage in the precordial leads. Negativity (diphasism \pm) of the T wave is shown in all the precordial leads.

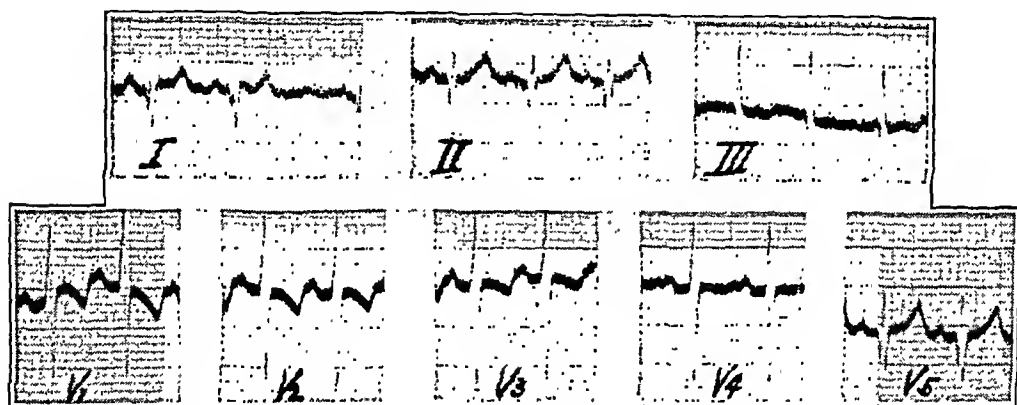


Fig. 4.—Electrocardiogram of a 20 day old child. The R and S waves are of nearly equal voltage in V_1 and V_2 .

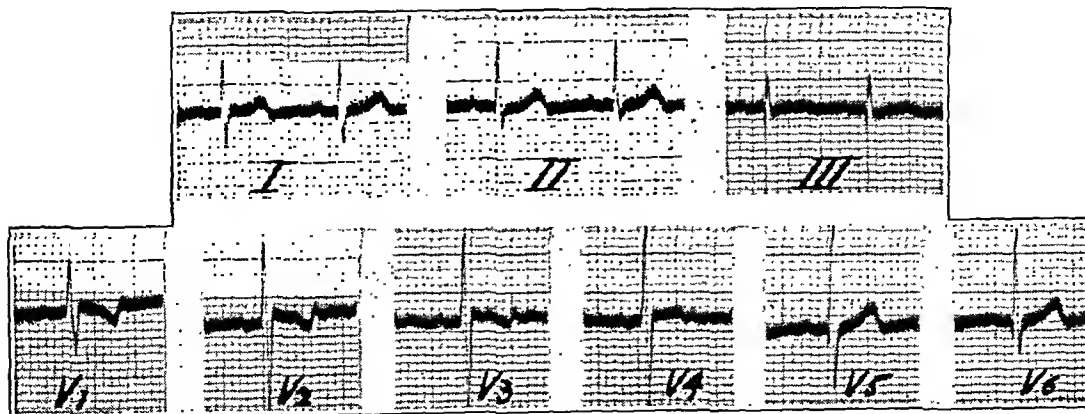


Fig. 5.—Electrocardiogram of a 4 year old child. The R wave increases up to V_6 ; the S wave increases up to V_4 and decreases in V_5 and V_6 . The T wave in V_1 , V_2 , V_3 and V_4 is diphasic.

Group B (3 to 5 Years).—This group showed the following characteristics:

- (1) Absence of Q up to V_3 , as in group A.
- (2) R wave of appreciably less amplitude in V_1 than in group A, increasing progressively in V_2 , V_3 , V_4 and V_5 , and decreasing in V_6 .

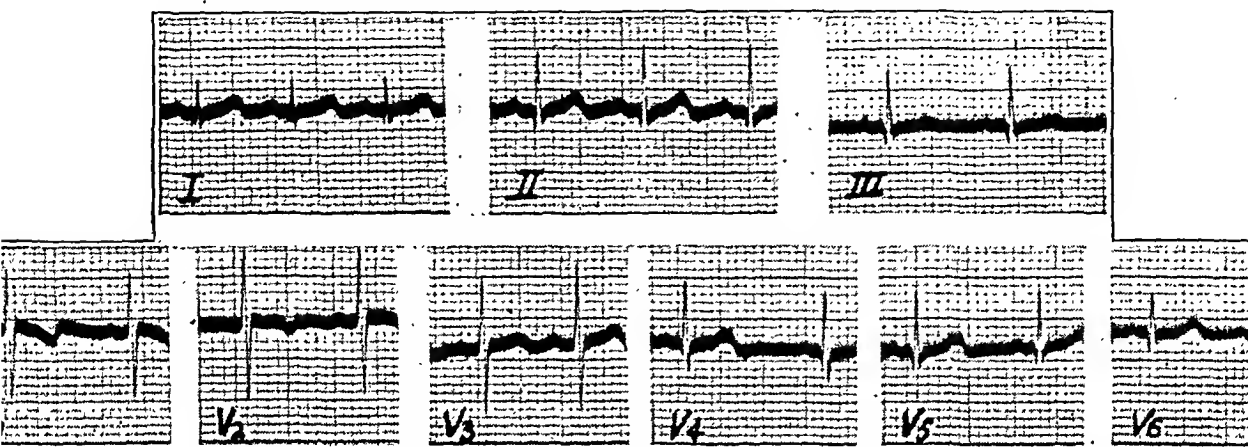


Fig. 6.—Electrocardiogram of a 3 year old child. The R and S wave are of nearly equal voltage in V_1 , V_2 and V_3 . The T wave is negative in V_1 and V_2 .

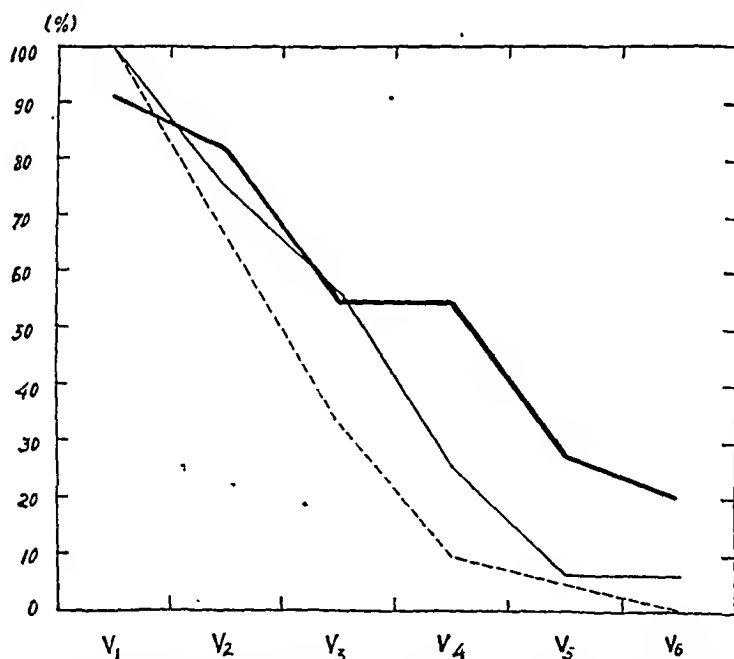


Fig. 7.—Frequency of the diphasic T waves in groups A, B and C. The wide black line is for children from birth to 2 years of age; the narrow black line for children from 3 to 5 years of age, and the broken line for children from 6 to 10 years of age.

- (3) The S wave to a certain extent similar to that of the adults. It was of less amplitude in V_1 and V_2 and increased comparatively after V_3 until it exceeded the size found in the adult. In V_6 , however, its size was smaller than that of the S wave in the adult (fig. 5).

(4) T wave with similar characteristics to that of group A, although its negativity was much more unusual in V_5 and V_6 (5 per cent).

Certain equilibrium or isodiphasism between R and S may be frequently observed in the right precordial leads in this group (fig. 6).

*Group C (6 to 10 Years).—*In this group were observed:

(1) Absence of Q up to V_2 as in adults.

(2) R wave of smaller amplitude in V_1 but increasing more evidently than in the former group up to V_4 and resembling what is commonly seen in the adults (fig. 6).

(3) S of higher voltage than R. The modifications undergone by this wave in the precordial leads resemble those occurring in adults, although the changes of height are not so definite.

(4) The T wave was found to be positive in the points to the left of the sternum but the negativity or diphasism of the T wave may be present in 10 per cent of the cases in V_4 .

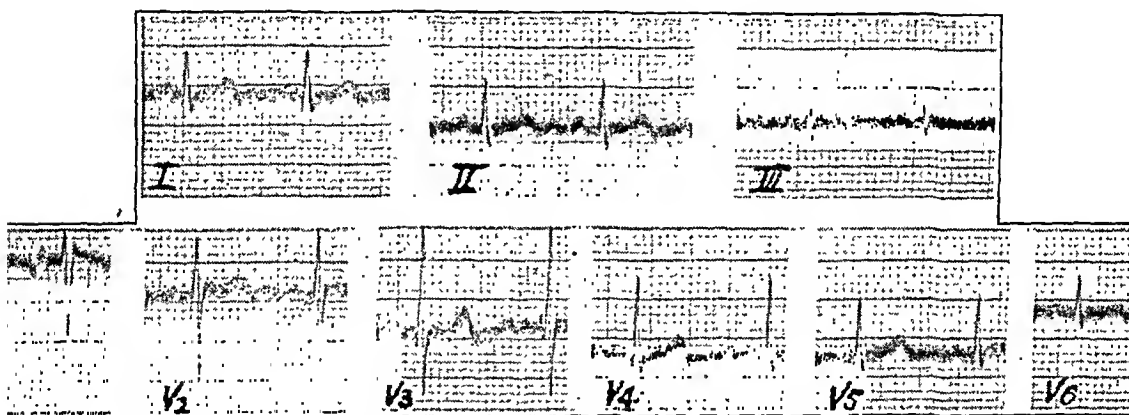


Fig. 8.—Electrocardiogram of a 7 year old child. It resembles the adult type.

A peculiarity that concerns the three groups is that in the precordial leads V_1 to V_6 the negativity of T observed in one lead is seldom more pronounced in the following ones; on the contrary, it generally decreases except in the transition from V_1 to V_2 .

Figure 7 shows the frequency of negativity or diphasism of the T wave, according to age.

COMMENT

In group A, the R wave was many times found greater than S in V_1 ; this predominance of the R wave frequently persists up to V_5 , differing thus appreciably from the precordial electrocardiogram of the adult. In group B, the R and S waves tend to be of equal amplitude in the leads to the right. They represent a form of transition between the former group (A) and the following (C). In group C the relative size of R and S is fairly similar to the "adult type," with definite predominance of S over R in V_1 and of R over S in V_6 .

As regards the behavior of the T wave, it is clearly illustrated in the corresponding diagram.

In the course of years the precordial electrocardiogram of children shows more and more the characteristics observed in the adult, so that it seems apparent that its gradual changes are related to the general development, and especially to the growth of the heart. Concerning this, the changes of position of the heart, its relations with the thorax and the cardiac configuration are of primary importance.

Regarding its position and relations with the thorax, the heart of the child has the following peculiarities:

- (1) Greater proximity of the heart to the thoracic wall.
- (2) Greater thinness of the thoracic wall.
- (3) Greater surface of contact between the thoracic wall and the right ventricle.
- (4) No interposition of the lung between the heart and the wall of the thorax.
- (5) More elevated diaphragm and consequently more horizontal position of the heart; this inclination begins to lessen between 6 and 12 months of age due to the unequal growth of the thoracic wall in relation to the growth of the lungs and the spine. The gradual lowering of the diaphragm contributes to the subsequent verticalization of the heart.

As regards the influence of the cardiac configuration on the electrocardiogram of the child, one must remember the proportions between the different cardiac cavities and their subsequent modifications.

In the beginning of extrauterine life the auricles are greater than the ventricles. The size and thickness of the right and the left ventricles are practically the same. At the age of 6 years the right ventricles maintain their initial thickness (3 to 4 mm.), while the thickness of the left ventricles has increased gradually to 8 mm.

It has been determined that in the newly born the ratio of the weight of the left ventricle to that of the right ventricle is 1:3, against 2:26 in the adult.

Concerning the spreading of the electrical impulse one should remember that the activation of the subendocardial region takes place rapidly because it is supplied by a special system of fibers for the conduction of the stimulus (Purkinje tissue). Then the myocardial wall is activated from the subendocardium to the subepicardium. As the conduction of this impulse is made by the cardiac fibers the activation here requires more time. The unipolar electrode placed in a point near the subepicardial region records the currents coming to it, and those leaving it as well, the former as a positive wave (R), the latter as a negative wave (S).

If one considers for instance the position V_1 in the adult, the walls of the right ventricle being appreciably less thick than those of the left, its activation is completed before that of the left (in spite of beginning almost simultaneously in both ventricles). Then the intrinsic R wave of relatively small amplitude is followed by the S. wave (which is the exponent of all the points of the left ventricle not yet activated), and the greater the thickness of the walls of this ventricle, the more important will be the voltage of the S wave. The inverse result is observed in V_6 , and in the intermediate points a range of transitional configurations will be observed.

The variations of the precordial electrocardiogram of children will thus depend on the aforementioned circumstances, among which we assign the greatest importance to the unequal development of both ventricles.

In group A, owing to the relative hypertrophy of the right ventricle there is a predominance of the R over the S wave in the points to the right. In group B, in which the predominance of the left ventricle begins to make itself evident, the tendency to isodiphasism R/S is the most outstanding peculiarity.

The negativity of the T wave can also be explained as a result of the different thickness of the ventricles, which modifies the repolarization of the ventricular wall.

In certain pathologic conditions in the adult, associated with hypertrophy of the right ventricle, the T wave becomes negative in the points "to the right"; moreover, the records are very similar to those of groups A and B owing to the simultaneous increased voltage of R.

The physiologic elevation of the diaphragm in children with the corresponding repercussion on the position of the heart is another factor probably influencing the negativity of T. This would be somewhat similar to what happens to a woman in the last months of pregnancy or during a deep complete expiration, when an inversion of the T IV is apt to occur (Master⁶).

The predominant belief that the T wave may be either positive or negative at the apex (T IV) has induced some authors to attribute little diagnostic significance to the precordial electrocardiogram of the child.

The variability of its shape in the different precordial leads and the modifications related to age make it necessary to record it in all the precordial points in order to be able to determine its diagnostic value.

SUMMARY AND CONCLUSIONS

1. The precordial electrocardiogram of a child differs from that of the adult in the characteristics of the QRS complex and of the T wave.

2. The gradual changes undergone by the child's electrocardiogram until it reaches the "adult" type are especially due to the cardiac development.

3. The following are the peculiarities shown by the three groups:

Group A (0 to 2 years): (a) Predominance of R over S in V_1 ; (b) frequency of negativity or diphasism of the T wave even up to point V_6 .

Group B (3 to 5 years): (a) Tendency to isodiphasism of R and S to the right; (b) negativity or diphasism of T up to V_6 although less frequently than in the former group.

Group C (6 to 10 years): (a) Predominance of S over R in V_1 as in the adult; (b) absence of negative T wave in V_5 and V_6 , inversely to what is observed in groups A and B.

4. The degree of negativity of T usually decreases gradually in the three groups from points V_1 to V_6 with the exception of V_2 , in which the negativity sometimes was greater than in V_1 .

5. For the correct interpretation of precordial leads in children the record of all the precordial leads is required.

FATAL MERCURIAL POISONING FOLLOWING PROLONGED ADMINISTRATION OF MERCUROPHYLLINE

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SINCE the introduction of organic mercurial diuretics about twenty-five years ago¹ innumerable injections of such compounds as merbaphen (U. S. P. XI), mersalyl and mercuriohylline have been given. Although toxic reactions have been reported they are amazingly few compared to the huge quantities administered. DeGraff and Nadler² summarized the literature on toxic manifestations of mercurial diuretics. They reported 26 deaths in sixteen years. No deaths have been reported from administration of the diuretics intramuscularly. Toxic reactions reported fall into three groups. Some reactions were due to the profuse diuresis.³ Other reactions or death followed suddenly after one or two doses of mercurial diuretics.⁴ These were probably the anaphylactoid reaction which might be due to any foreign agent. In some cases, mersalyl apparently caused tubular damage to the kidney.⁵

This case is being reported because, as far as can be determined, it is the first in which there was a mercurial toxic nephrosis with anuria

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1. Saxl, P., and Heilig, R.: Ueber die diuretische Wirkung von Novasurol und anderen Quecksilberinjektionen, *Wien. klin. Wchnschr.* **33**:943, 1920.

2. DeGraff, A. C., and Nadler, J. E.: A Review of the Toxic Manifestations of Mercurial Diuretics in Man, *J. A. M. A.* **119**:1006 (July 25) 1942.

3. Klinghoffer, K. A.: Dehydration from Diuretics, *Internat. Clin.* **1**:221 (March) 1941. Poll, D., and Stern, J. E.: Untoward Effects of Diuresis. *Arch. Int. Med.* **58**:1087 (Dec.) 1936.

4. Cadbury, W. W.: Idiosyncrasy to Salyrgan, in *Medical Papers Dedicated to Henry Asbury Christian, Physician and Teacher, in Honor of His Sixtieth Birthday, February 17, 1936*, Baltimore, Waverly Press, Inc., 1936, p. 259. Marvin, H. M.: Merbaphen (Novasurol) as a Diuretic in Congestive Heart Failure, *J. A. M. A.* **87**:1016 (Sept. 25) 1926. Sprunt, D. H.: Renal Damage Following Administration of Merbaphen (Novasurol), *Arch. Int. Med.* **46**:494 (Sept.) 1930. Wolf, I. J.: Idiosyncrasy to Salyrgan, *J. A. M. A.* **102**:1177 (April 7) 1934.

5. Rosenthal, M.: The Anatomic Lesions of Fatal Mercurial Intoxication from Salyrgan, *Arch. Path.* **15**:352 (March) 1933. Tarr, L., and Jacobson, S.: Toxicity of Mersalyl (Salyrgan), *Arch. Int. Med.* **50**:158 (July) 1932.

and death after the usual course of repeated parenteral injection of mercurophylline.

REPORT OF A CASE

A white woman, 35 years old, was admitted to the Long Island College Hospital on June 2, 1945, for edema of six months' duration. However, the patient had had dyspnea and had been treated with digitalis for twenty years. At 11 she had had chorea, which recurred every year for four years. Then she had several attacks of febrile polyarthrits. From December 1944 to May 20, 1945, she received about 12 injections of mercurophylline with good results; a dose two days before entry had not effected the usual diuresis.

She was an orthopneic, obese woman with a blood pressure of 160 mm. of mercury systolic and 100 diastolic and gave typical evidence of mitral stenosis and auricular fibrillation. The edge of the liver was tender and came 12 cm. caudal to the right costal margin. There was pitting edema of the legs, thighs and sacral region.

She had a trace of protein in the urine, but no casts or red cells; the blood urea was 25 mg. per hundred cubic centimeters, and the glucose, cholesterol, albumin, globulin and hemoglobin were within the normal range. An electrocardiogram was that of a myocardial disease pattern consistent with a clinical diagnosis of mitral stenosis.

On a diet containing very little salt and 1,500 calories per day with digitalis and intravenous mercurophylline injections, 2 cc. every three to five days, her weight fell from 183 (83 Kg.) to 143 pounds (64.9 Kg.) in one month. She was practically free of symptoms and returned to her home. There she received the same dose of mercurophylline intramuscularly once a week, but since there was no real diuresis after the fifth dose, the injection was repeated three days later. After this, oliguria was considerable, edema developed rapidly, and on the third day, after twelve hours of anuria and dull pain in both flanks, she reentered the hospital.

Physical Examination.—The patient on examination was alert, extremely apprehensive but not dyspneic. She had a puffy face and prominent eyes ("nephrotic stare"). Her blood pressure was 135 systolic and 100 diastolic, but subsequent readings could not be obtained because of the edema. The apical rate was 120 per minute and totally irregular, and there was a pulse deficit of 50. Her temperature was 99 F. Fundoscopy showed tortuous veins, but no exudates, hemorrhages or papilledema. The lungs were clear to percussion and auscultation. Her heart was essentially unchanged from the previous entry. The edge of the liver was 7 cm. below the costal margin. The tip of the spleen could be felt. All extremities, thorax, abdomen and face showed considerable pitting edema. There was minimal cyanosis of the nail beds.

Catheterization yielded approximately 8 cc. of turbid, yellow urine, which showed an extreme proteinuria, p_H of 6, 4 white cells, 3 red cells and an occasional granular cast per high power field in the uncentrifuged specimen.

An infusion of 10 per cent glucose in distilled water was started, but because of the considerable edema the infusion occasionally infiltrated the tissues, and during the first eighteen hours only 2,000 cc. were administered. Gradually her extremities became gray, cold and clammy. She complained of sharp pain in both flanks, radiating around to the lower abdominal quadrants.

Her urea nitrogen was 55 mg. per hundred cubic centimeters, and blood urea was 119 mg. per hundred cubic centimeters. An infusion of 20 per cent dextrose

in water was started. Twenty-two hours after the patient's admission a bilateral renal decapsulation was performed with gas-oxygen-ether anesthesia. At operation the capsule of the kidney was very tense. When the capsule was slit the swollen enlarged congested kidneys quickly bulged through. She withstood the operation well, but her face remained flushed. Her extremities were cyanotic and cold. Her blood pressure could not be determined. The pulse was 110 per minute, respirations 30 per minute, temperature 98 F. Postoperatively she received 500 cc. of plasma.

Six hours after operation catheterization yielded 8 ounces (227 cc.) of urine showing considerable albuminuria, hyaline-granular casts and red and white blood cells. The specific gravity was 1.008. Four hours later 4 ounces (113.4 cc.) was obtained of similar composition. However, the patient remained prostrate and semicomatose, and died three hours later.

Postmortem Examination (Seven Hours After Death).—Gross Examination. The body was that of a well developed, somewhat obese, white woman. There was no pertinent information obtained from the external examination except that there was moderate pitting edema of the lower extremities and a large operative incision in each flank.

The pleural cavities each contained 100 cc. of clear yellow fluid. The pericardial cavity contained 30 cc. of clear yellow fluid.

The heart weighed 620 Gm. The left auricle was dilated and the mitral valve was greatly thickened and nodular, with fusion of the valve cusps. The chordae tendineae were thickened and inserted on the under border of the valve. The papillary muscles were considerably hypertrophied, as was the left ventricular wall. The tricuspid valve was similarly involved but to a lesser degree. The aortic valve was not unusual.

The lungs were not edematous, but there were a few small patches of bronchopneumonia.

The peritoneal cavity contained 500 cc. of slightly turbid sanguineous fluid. On the serosal surface of the ileum and large intestine there were focal areas of purple discoloration. The kidneys were in the usual retroperitoneal position, but both capsules had been split.

The essential findings observed in the abdomen were confined to the liver, kidneys and intestines. The liver weighed 2,150 Gm. and was smooth and firm. The cut surface was mottled and yellow-red, and there were several large, focal, hemorrhagic areas measuring 3 cm. to 4 cm. in diameter. The kidneys weighed 350 Gm. each and measured 14 by 9 by 5 cm. They were distinctly swollen, very pale and tan. The cortex was widened, pale and fairly well demarcated from the pale red medullary pyramids. The intestines were not remarkable except for several large areas of hemorrhage in the mucosa of the ileum and colon. There was no urine in the bladder.

Histologic Examination: The microscopic study revealed the following pertinent facts. The heart was noticeably hypertrophied, and there was a moderate perivascular interstitial fibrosis, but there were no Aschoff bodies. There were small areas of bronchopneumonia in the lung. There was chronic passive congestion of the spleen, pancreas and liver.

Sections of the kidney revealed that the general architecture of the kidney was well preserved. The glomeruli were prominent and showed a slight increase in fibrous tissue, but there was no evidence of congestion, atrophy or hyalinization. There was a moderate amount of granular material in Bowman's space. The proximal convoluted tubules showed varying degrees of cellular damage

from cloudy swelling to complete necrosis. A majority of the tubules were patent but moderately filled with an amorphous, eosinophilic granular material. Some cells were swollen and contained granular cytoplasm with large, round, vesicular nuclei, but there were large numbers of the proximal convoluted tubules in which the cellular outlines were lost and the nuclei were absent or pyknotic (fig. 1). This necrosis extended throughout the proximal convoluted tubule. The distal convoluted tubules and collecting tubules were for the most part uninvolved. There were several areas in which small tubules were seen with cuboidal epithelium, hyperchromic elongated nuclei and an occasional mitotic figure. These are regenerating tubules (fig. 2). There was a moderate increase in the interstitial

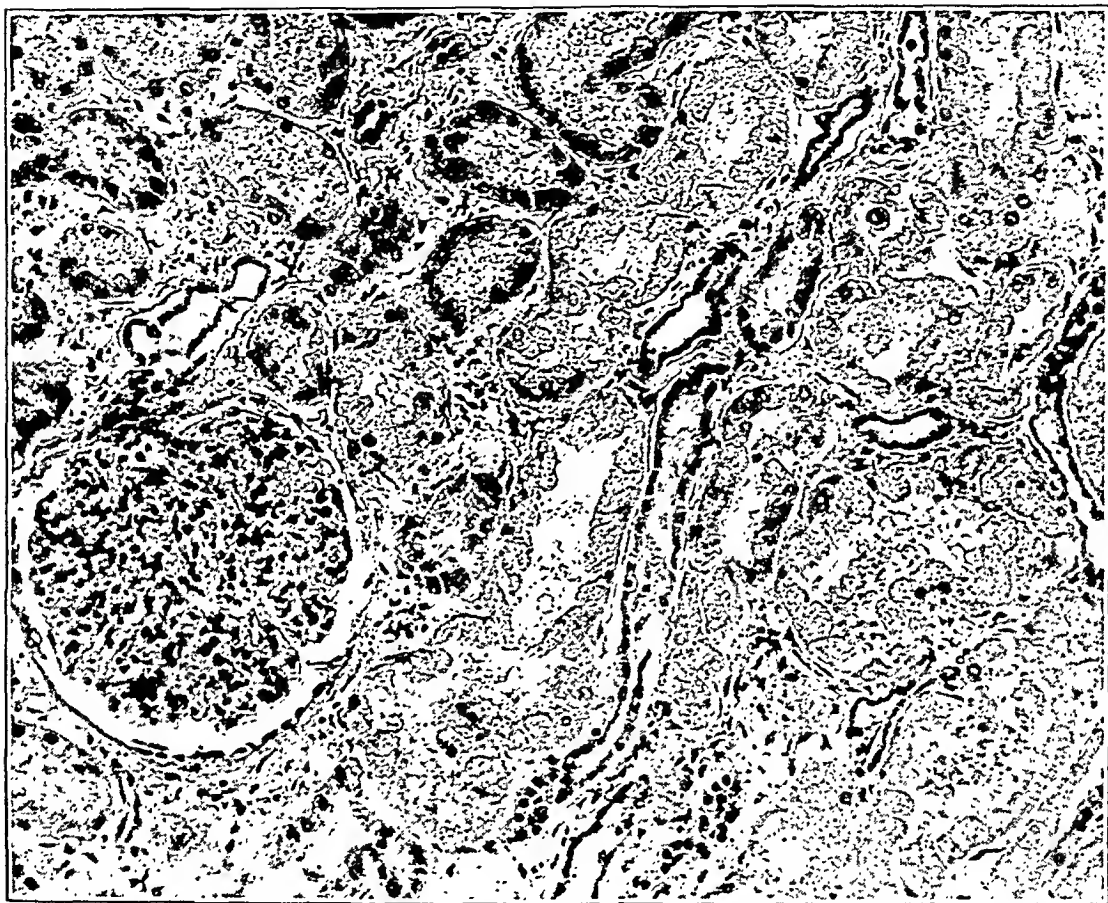


Fig. 1.—The cells of the proximal convoluted tubules are swollen with necrosis of some cells and the absence or pyknosis of many nuclei (\times approximately 205).

fibrous tissue. The blood vessels were moderately dilated, and some of the larger vessels had thickened walls which were partially hyalinized. A sudan III stain of the kidney demonstrated in scattered areas a minimal amount of fatty degeneration in the damaged tubule.

The sections taken from the hemorrhagic areas in the liver demonstrated moderate changes. The general architecture of this portion was obscured because of recent hemorrhage into the liver with necrosis of the hepatic cells. The sinusoids were considerably congested. In these areas some of the hepatic cells had lost the cellular outline, while others had but a thin granular eosinophilic network with pyknotic or absent nuclei. There was moderate fibrous infiltration

into the periportal areas. The sections taken from other areas in the liver revealed but minimal degeneration, with the same moderate fibrosis throughout the liver in the periportal areas and with some regeneration of bile ducts. A sudan III stain of the liver demonstrated no fatty change, but a Maasson trichrome stain showed the collagenous fibrosis of the periportal areas.

There were no other contributory conditions observed and permission for the examination of the brain and spinal cord was denied.

Anatomic Diagnosis: (1) Rheumatic heart disease with mitral and tricuspid stenosis; (2) chronic passive congestion in the liver, spleen, pancreas, kidney; (3) poisoning due to mercuriophylline; (4) nephrosis, toxic, of the kidney;



Fig. 2.—This shows the regeneration of tubules with low cuboidal epithelium and hyperchromic elongated nuclei. A mitotic figure may be seen near the center of the photograph (\times approximately 368).

(5) necrosis, toxic, of the liver; (6) hemorrhage in the ileum and colon, and (7) bronchopneumonia—terminal were diagnosed.

Qualitative Chemical Analysis: On 10 Gm. of tissue the Reinsch test and the confirmatory Gettler test for mercury were performed, and mercury was demonstrated to be present in the kidney.⁶ On 20 Gm. of liver similar tests were performed which elicited faintly positive reactions for mercury.

6. Simmons, J. S., and Gentzkow, C. L.: *Laboratory Methods of the United States Army*, ed. 5, Philadelphia, Lea & Febiger, 1944, pp. 335-336.

COMMENT

It appears certain that mercurophylline was responsible for the outcome in this case. The presence of mercury at the site of damage in the kidneys and liver was demonstrated by chemical analysis. This factor, plus the characteristic pathologic evidences of tubular necrosis and hemorrhage in the ileum and colon, substantiates mercury as the causative agent. Although there was no calcification in the tubules, this does not eliminate mercury as the cause of the nephrosis, as calcification does not occur in many of the kidneys damaged by mercuric chloride. Regeneration of tubules with hyperchromic nuclei and poorly staining cytoplasm, with an occasional mitotic figure, is not uncommon in diffuse kidney disease and has been seen after the experimental use of mercury to induce nephrosis.⁷ Therefore, mercurophylline in this case has produced a pathologic picture similar to that of poisoning by mercuric chloride.

The damage to the hepatic cells may possibly result from extreme passive congestion, but because of the severity of the process, the presence of mercury in the liver and the characteristic finding of mercuric poisoning in the other organs, it seems likely that mercury was responsible for this damage.

The problem of treatment in a case of anuria is still unsettled. Large amounts of fluid are usually administered, although there is some evidence that restriction of fluid intake and bilateral renal decapsulation may be of value. This issue has been recently reopened by Peters,⁸ who believes that an increase in intrarenal pressure is the factor which inhibits the flow of urine and not tubular blockage by detached necrotic cells or low arterial blood pressure. This patient was temporarily benefited by renal decapsulation. But until the mechanism of anuria is more clearly understood there will be evidence for and advocates of both methods of treatment.

The undesirable and even fatal effects which occasionally follow use of mercurial diuretics are well known, and the physician naturally takes precautions to minimize the hazards, particularly those which seem due to acquired sensitivity. These agents are, unfortunately, the most effective means now available to remove salt and water from patients in whom these substances are excessively retained, and their use will be widespread and in some cases continuous over many years. One patient⁹ has taken as much as 1,250 cc. in 627 injections, and

7. Oliver, J.: Histogenesis of Chronic Uranium Nephritis, *J. Exper. Med.* **21**:425, 1915.

8. Peters, J. T.: Oliguria and Anuria Due to Increased Intrarenal Pressure, *Ann. Int. Med.* **23**:221 (Aug.) 1945.

9. Friedenson, M.: The Prolonged Use of Mercurial Diuretics in Heart Failure, *Ann. Int. Med.* **20**:306 (Feb.) 1944.

others have taken hundreds of injections with only beneficial results. Until patients can be given satisfying sodium-free diets, or until better agents are developed for removing retained sodium, physicians will continue to use the mercurial diuretics.

SUMMARY

A case is reported of a 35 year old woman with rheumatic heart disease and cardiac decompensation, who received mercurophylline parenterally for six months, and who developed an acute anuria, fatal in spite of bilateral decapsulation of the kidney. Postmortem examination revealed nephrosis, hemorrhage in the ileum and colon and focal areas of necrosis and hemorrhage in the liver. Mercury was found in the liver and kidney. The death was attributed to mercurial intoxication.

Note.—Since this article was submitted for publication a similar case of toxic nephrosis due to mercurophylline has been the subject of a clinicopathologic case report (Cabot Case 31451, *New England J. Med.* **233**:567 [Nov. 8] 1945).

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INFECTIOUS MONONUCLEOSIS

A Consideration of the Complications and a Preliminary Report on the Use of Penicillin in This Disease

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RENEWED interest in the diagnosis of infectious mononucleosis has developed since the introduction of the Paul-Bunnell test in 1932.¹ Although a positive heterophile antibody reaction is not essential in making the diagnosis of this disease, the reaction is almost pathognomonic when positive. The early or frequent use of this test may establish a diagnosis when the clinical signs are confusing or before suggestive or diagnostic changes in the white blood cells have occurred; however, it may not be positive during the acute phase of the disease, nor is it necessarily related to the changes in the blood picture. Blood smears and Paul-Bunnell tests may have to be repeated several times before the diagnosis is established. Usually these procedures are not frequently repeated in the management of private patients because of the expense involved. This becomes even more apparent should the patient have a mild form of the disease. It seems probable, therefore, that many cases of infectious mononucleosis are incorrectly diagnosed as influenza, tonsillitis, sore throat, Vincent's angina or some other benign disease.

Epidemics of infectious mononucleosis have been reported; in 1943 an account of an epidemic in an Emergency Medical Service hospital in Scotland was reported by Halcrow, Owen and Rodger² in which 290 cases of infectious mononucleosis were detected. In 125 of these the patients were ill enough to have clinical symptoms, but in 165 cases the patients had a subclinical form of the disease, which was discovered only by doing blood smears and establishing the presence of a positive heterophile antibody reaction. This is surprising when one considers that 57 per cent of these patients were not clinically ill. Press, Shlevin and Rosen³ listed 36 presenting symptoms in their series of cases. Text-

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1. Paul, J. R., and Bunnell, W. W.: The Presence of Heterophile Antibodies in Infectious Mononucleosis, *Am. J. M. Sc.* **183**:90-104 (Jan.) 1932.

2. Halcrow, J. P. A.; Owen, L. M., and Rodger, N. O.: Infectious Mononucleosis with an Account of an Epidemic in an E.M.S. Hospital, *Brit. M. J.* **2**:443-447 (Oct. 9) 1943.

3. Press, J. H.; Shlevin, E. L., and Rosen, A. P.: Infectious Mononucleosis: A Study of Ninety-Six Cases, *Ann. Int. Med.* **22**:546-562 (April) 1945.

books and medical journals mention the milder forms of the disease, but the usual description includes headache, malaise, fever, sore throat, enlarged spleen and lymph nodes, with possibly a rash, meningeal signs or jaundice, accompanied with changes in the white blood cell elements and a positive reaction to the Paul-Bunnell test. Evidence is now accumulating which indicates that this clinical picture represents the severer form of the disease.

An infectious disease which shows such a wide range in severity and which may present a great variety of symptoms is often difficult to diagnose. Benign as it is, it is set apart from the usual infectious or contagious disease when one is confronted with an acutely ill patient concerning whom observations are confusing and laboratory reports do not reveal any abnormalities. The severity of the acute phase in some cases often leads one to abandon the diagnosis of infectious mononucleosis if there is no suggestive or confirmatory support from the laboratory. Later, as the patient improves, the diagnosis becomes established. From time to time authors ⁴ on this subject have separated cases of infectious mononucleosis into types according to the predominant symptoms and physical observations. These classifications of the disease reflect its protean nature. In such an infectious disease it is sometimes difficult to decide which symptoms are part of the disease and which may be arising from the complications which occur.

Ulcerative pharyngitis and tonsillitis occurring in infectious mononucleosis have been described so frequently that these conditions have come to be regarded by many as a symptom of the disease. Sore throat is undoubtedly one of the commonest symptoms, and many patients have it in some degree sometime in the course of their illness. Contratto ⁵ stated that sore throat was present in 82 per cent of 196 cases; and Press, Shlevin and Rosen ³ reported sore throat in 68.7 per cent of 96 cases. However, in both of these large series of cases the occurrence of ulcerative pharyngitis and tonsillitis was relatively low—22 per cent in Contratto's cases. In the series of cases reported by Press and his colleagues, the incidence of tonsillitis was not given, but they did not observe a single case of ulcerative pharyngitis or Vincent's stomatitis. Halcrow and his colleagues ² found sore throat in 35 of the 125 patients who were clinically ill, but only 4 had the "anginose" type. Read and Helwig, ⁶ in

4. (a) Cecil, R. L.: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1944, p. 464. (b) Walker, W. H.: Infectious Mononucleosis, Bull. U. S. Army M. Dept., December 1944, no. 83, pp. 80-93.

5. Contratto, A. W.: Infectious Mononucleosis: A Study of One Hundred and Ninety-Six Cases, Arch. Int. Med. **73**:449-459 (June) 1944.

6. Read, J. T., and Helwig, F. C.: Infectious Mononucleosis: An Analysis of Three Hundred Cases with Three Characterized by Rare Hematologic Features Arch. Int. Med. **75**:376-380 (June) 1945.

an analysis of 300 cases, reported 150 (50 per cent) cases of the anginose type, but membranous pharyngitis occurred in only 34 cases (11 per cent), and acute tonsillitis occurred in only 29 cases (10 per cent). The combined cases were 21 per cent. Although sore throat is part of the disease, ulcerative pharyngitis, follicular or ulcerative tonsillitis and Vincent's stomatitis should be regarded as complications. In most cases specific virulent organisms are present, such as streptococci, pneumococci, fusiform bacilli and spirochetes. When these complications occur as the presenting symptoms they often mask any other complaints. When occurring after the diagnosis of infectious mononucleosis has been established, they are frequently more disabling than the disease itself, even though the acute phase may have been quite severe.

Since the origin of infectious mononucleosis is unknown, no specific therapy has been developed. A virus is suspected,⁷ but the disease has not been consistently reproduced in man or in laboratory animals. Assuming that the causative agent is a virus, it would not be expected that sulfonamide therapy or penicillin would be of benefit. One case of infectious mononucleosis was reported⁸ to have developed in a patient who was undergoing an intensive course of penicillin therapy while being treated for osteomyelitis. Recently, authors⁹ of papers on penicillin have listed infectious mononucleosis as one of the diseases in which penicillin should not be used. This attitude regarding the use of penicillin in infectious mononucleosis is logical, but unfortunately it has been too closely followed, with the result that penicillin is not being used in any phase of the disease. The commonest and also one of the severest complications seen in infectious mononucleosis is sore throat or tonsillitis which is caused by the invasion of the host by well known organisms, and it is expected that penicillin, and to a much smaller extent, sulfonamide drugs, would be of considerable value in these conditions. Penicillin and sulfadiazine were used in the treatment of some of our patients. Although the number of patients treated with penicillin are few, there was only 1 who did not respond dramatically when penicillin was used in infectious mononucleosis to treat those complications which are frequently considered a part of the disease per se.

The incidence of sporadic cases of infectious mononucleosis is higher than would be expected when compared to other well known diseases

7. Julianelle, L. A.; Bierbaum, O. S., and Moore, C. V.: Studies on Infectious Mononucleosis, *Ann. Int. Med.* **20**:281-292 (Feb.) 1944.

8. Bloomfield, A. L.; Kirby, W. M. M., and Armstrong, C. D.: A Study of "Penicillin Failures," *J. A. M. A.* **126**:685-691 (Nov. 11) 1944.

9. Herrell, W. E.; Nichols, D. R., and Heilman, D. H.: Penicillin: Its Usefulness, Limitations, Diffusion and Detection, with Analysis of One Hundred and Fifty Cases in Which It Was Employed, *J. A. M. A.* **125**:1003-1010 (Aug. 26) 1944. Bloomfield, Kirby and Armstrong.⁸

affecting the same age group. It is probable that there have been cases of infectious mononucleosis misdiagnosed because it too closely resembled some other disease, and with this thought in mind the histories of all cases of acute follicular and ulcerative tonsillitis, Vincent's angina and infectious hepatitis occurring in 10,000 consecutive hospital admissions were reviewed to determine whether those particular records contained clinical or laboratory evidence suggestive of infectious mononucleosis. There were among those 10,000 cases 31 sporadic cases of infectious mononucleosis, 25 cases of infectious hepatitis, 51 cases of Vincent's angina and 307 cases of acute tonsillitis.

ACUTE FOLLICULAR OR ULCERATIVE TONSILLITIS

There were 307 admissions with a diagnosis of acute follicular or ulcerative tonsillitis, but white blood cell counts were done in only 175 cases, and only those cases were considered. Among the 175 cases of tonsillitis there were 15 cases in which the differential white blood cell count revealed either a moderate or pronounced preponderance of the monocytic series; a specific mention was made of the presence of abnormal lymphocytes, or the total white blood cell count (disregarding the differential count) was less than 9,000 in the presence of a temperature higher than 102 F. (38.9 C.). In the latter group of cases the temperature was more often 103 F. (39.4 C.) or higher. In not one of these cases was infectious mononucleosis suspected, and Paul-Bunnell tests were not made during the time the patients were hospitalized; however, 1 patient, whose case is not included among the 15, was readmitted to the hospital one week later with generalized enlargement of the lymph nodes, and the reaction to the Paul-Bunnell test was positive in a 1:160 dilution on admission. The blood counts or the clinical course during his tonsillitis did not reveal anything suggestive of infectious mononucleosis, as shown by his chart; this leads one to wonder what more suggestive evidence of infectious mononucleosis need be present besides the suspicion.

Throat smears or throat cultures were done in 77 cases. The majority, 45, contained nonhemolytic streptococci. There were 9 in which Vincent's organisms were present but not thought to be the causative agent, and in the remainder no pathogenic organisms were found.

VINCENT'S ANGINA

Among the 10,000 cases there were 52 cases of Vincent's angina. It is generally accepted that the symbiotic organisms *Borrelia vincenti* and *Fusobacterium plauti-vincenti* may be found in the mouths of apparently healthy persons, and no discussion as to their pathogenicity will be made; suffice it to say that the diagnosis of this disease was made in conformity with generally accepted principles. These cases were likewise studied in search for evidence suggestive of infectious mononucleosis.

When applicable the same factors were considered. In almost all of the cases there was either a membranous pharyngitis or tonsillitis. Of the 52 cases white blood cell counts were not done in the first 19 because of inadequate laboratory facilities. Of the 33 remaining cases, in which total and differential white blood cell counts were done, there were only 2 cases suggestive of infectious mononucleosis. This incidence was surprisingly low. In both cases Paul-Bunnell tests were done, one before the patient's discharge from the hospital and the other eight days following the patient's discharge. In both cases reactions to the Paul-Bunnell tests were negative. In many of the cases there were enlarged cervical lymph nodes, but there was no mention of enlarged nodes elsewhere. In only 39 cases were throat smears done, and 35 of those were found to have reactions of 2 to 4 plus (on an arbitrary scale) for Vincent's organisms.

The most striking feature revealed in a review of the cases of Vincent's angina was the fact that, although a membrane was present in most cases and although the patients were ill enough to be hospitalized for an average of eleven days per patient, they seldom had a temperature of over 100.4 F. (38 C.). This absence of a high temperature in such cases is in sharp contrast to those cases in which Vincent's angina exists as a complication of infectious mononucleosis, in which the temperature is often much higher. In 43 of the 52 cases there was a temperature of less than 100 F. (37.8 C.).

INFECTIOUS HEPATITIS

This disease was considered because jaundice is occasionally present in infectious mononucleosis. Its frequency of occurrence is low. Caution was used in evaluating the significance of low white blood cell counts or the ratio of neutrophils and monocytes. Similar abnormalities in the blood may be present in infectious hepatitis and early in infectious mononucleosis. There were 25 cases of infectious hepatitis. There were 4 cases in which the observations were suggestive of infectious mononucleosis. In 1 of the 4 cases there was a total white blood cell count of 4,600, with 41 per cent neutrophils and 59 per cent cells of the monocytic series. The temperature of the patient was 102.4 F. (39 C.) on admission and remained above 101 F. (38.3 C.) for three days. Infectious mononucleosis was considered, but only one Paul-Bunnell test was done, and the reaction to it was negative. In 1 case the maximum white blood cell count was never over 4,000, with 44 per cent neutrophils and 56 per cent cells of the monocytic series. In this case the fever was 103.4 F. (39.6 C.), and an eruption was present for two days. Unfortunately, a test for the presence of heterophile antibodies was not done. Another case was even more striking; there was a white blood cell count of 10,750, with only 8 per cent neutrophils and with the remainder, 92 per cent, of the monocytic series.

INFECTIOUS MONONUCLEOSIS

The diagnosis of infectious mononucleosis was confirmed in all but 1 case by a positive reaction to the Paul-Bunnell test with a dilution of 1 : 40 or higher. Most often no further determinations were done after the first positive reaction was obtained. In any event the diagnostic criteria mentioned by Kaufman¹⁰ were present in each case.

There were 31 sporadic cases of infectious mononucleosis occurring in 10,000 consecutive hospital admissions. There was no recognized epidemic. These cases occurred within a period of twenty-three months. In the later months the medical staff became more interested in infectious mononucleosis, which resulted in more diagnoses being made and confirmed. In the first month after the case study was completed there were 6 cases diagnosed. This emphasizes the importance of looking for infectious mononucleosis in any ill defined infectious disease. This diagnosis was made in only 6 of the 31 cases at the time of admission. The duration of the disease at the time of admission varied from one to nine days, the average being four days. The onset of the complication ranged from one to sixteen days, the average being seven days. The number of days in the hospital for all patients varied from six to thirty-six, with an average of twenty; however, these patients were not released from the hospital until each was capable of performing full duty.

The clinical course varied. In 11 cases the highest temperature did not exceed 101 F. (38.3 C.), and neither tonsillitis nor membranous pharyngitis was present. In 12 of the 31 cases the temperature exceeded 104 F. (40 C.) and was of the daily remitting type accompanied by chills. Until the diagnosis was made, malaria, septicemia or diphtheria was often suspected. In arriving at the diagnosis in such cases, before the blood counts become suggestive of infectious mononucleosis or the reaction to the Paul-Bunnell test becomes positive, one is apt to look with doubt on the frequently written statement that this disease is benign.

The frequency and type of complication are of no statistical significance in this small group of cases but will be included for the sake of completeness. In 11 cases there was no complication. There was 1 case of otitis media and 1 case of albuminuria. Acute tonsillitis was present in 11 cases and ulcerative pharyngitis was present in 8 cases. Throat smears or cultures contained Vincent's organisms in 10 cases, hemolytic streptococci in 3 cases, and nonhemolytic streptococci in 2 cases.

No new information was learned from studying the white blood cell counts or the differential counts in relation to the onset of the complication, the height of the fever or the appearance of a positive reaction for

10. Kaufman, R. E.: Heterophile Antibody Reaction in Infectious Mononucleosis, *Ann. Int. Med.* **21**:230-251 (Aug.) 1944.

heterophile antibodies. No consistent correlation of these factors was present.

TREATMENT OF COMPLICATIONS

Sulfadiazine was used in many cases of sore throat and tonsillitis complicating infectious mononucleosis, but only those which received this form of medication in the usual dosages for at least two days were considered as having been adequately treated. There were 8 such patients. The response of 3 patients to sulfadiazine was considered good and for the remainder the results were equivocal. Of the last 7 patients of the series there were 4 sufficiently ill with ulcerative pharyngitis or tonsillitis and high fever to warrant the trial of penicillin. Three of the 4 patients had ulcerative pharyngitis, while the other had tonsillitis. These complications occurred nine, sixteen, eight and two days, respectively, after the onset of the disease. Vincent's infection was present in only 1 of the patients. Each of the patients had considerable involvement, complained bitterly of pain, and had a temperature from 102 F. to 104 F. (38.9 C. to 40 C.). For 3 of the 4 patients there was a dramatic improvement in the symptoms and appearance of the throat as well as a fall in temperature within twelve to twenty-four hours. The doses were 20,000 Oxford units given intramuscularly every three hours with an ice bag placed over the site of injection. The total dosages were from 160,000 to 460,000 units. In the patient who did not seem to respond so favorably the pharyngeal ulcers began to heal, but there was slow progress, and the temperature of 103.6 F. (39.7 C.) gradually subsided within three days. The throat culture revealed nonhemolytic streptococcus, and the smear was 4 plus positive for Vincent's organisms.

REPORT OF CASES

CASE 1.—A white officer, 24 years old, was admitted to the hospital March 2, 1945, complaining of chills, fever, malaise and headaches which had begun approximately five days before admission. The chills and fever occurred on February 26 and 28 and March 1, 1945. During the intervals between chills he felt fairly well and did not report for medical treatment. There had been no nausea, vomiting, diarrhea or abdominal pain, and he did not have a cough, sore throat or other symptoms of respiratory infection. The patient stated that he had been in Hawaii for a few days in October 1942 and had completed approximately one year of service in England about one year previously, returning to the United States in January 1944. He gave no history of having been exposed to infectious or contagious diseases. The past and familial history was irrelevant. This patient had had thirty-two months of duty on flying status and had been in good health except for minor respiratory infections.

The temperature on admission was 101.8 F. (38.7 C.). The skin was dry and he appeared to be acutely ill. The nose and throat were normal. He had considerable headache but there was no rigidity of the neck. No lymph nodes were palpable. There were no rales or dull areas in the lungs. The blood pressure was 115 systolic and 70 diastolic. The pulse was 112 and regular in rhythm.

The heart was not enlarged, there were no murmurs and the heart sounds were of good quality. Examination of the abdomen revealed the spleen to be barely palpable and tender. The liver was neither palpable nor tender. There was an appendectomy scar. The remainder of the examination of the abdomen revealed nothing abnormal. The superficial and deep reflexes were all normal.

For four days following admission, the patient had daily chills with temperature spiking to 104 F. or 105 F. (40 C. to 40.6 C.). Because of the enlarged, tender spleen and the lack of other signs, a tentative diagnosis of malaria was made on the second hospital day. The white blood cell count on admission was 6,400, with 72 per cent neutrophils and 28 per cent lymphocytes; there was no significant change during the first five days. Specimens of urine were normal. Thick and thin blood smears were repeatedly found negative for malarial parasites. However, in spite of the negative blood smears, 3 grains (0.2 Gm.) of quinacrine hydrochloride was given every six hours for five doses, starting on the second hospital day. The chills and high fever subsided on the fourth day, but a temperature of 101 F. to 102 F. (38.3 C. to 38.9 C.) persisted for three days. On the fifth

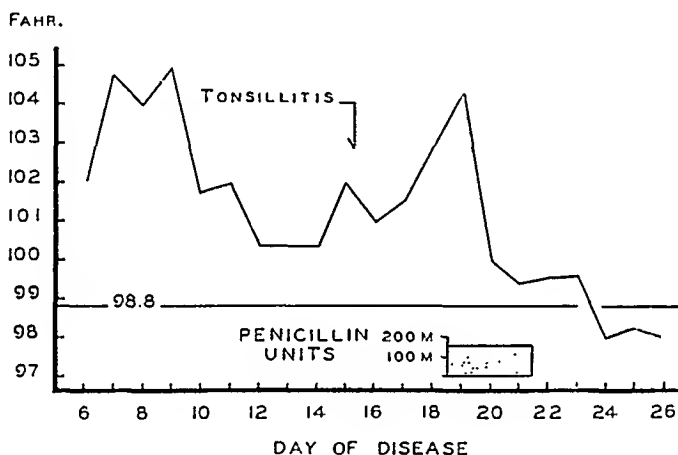


Fig. 1 (case 1).—The secondary rise of temperature is associated with the development of severe tonsillitis occurring in infectious mononucleosis, the so-called anginose type. The dramatic response to penicillin is illustrated by the abrupt drop in the temperature curve.

day small nontender lymph nodes were felt in the left posterior cervical triangle. The following day the spleen became definitely larger, and the diagnosis was changed to infectious mononucleosis, and quinacrine was discontinued. During this time there had been very little change in the white blood counts except for a slight increase in lymphocytes up to 45 per cent, with the total white blood cell count not exceeding 7,300. The Paul-Bunnell test elicited a negative reaction, and examination did not reveal abnormal lymphocytes in the blood smears. The Weil-Felix reaction was negative. On the seventh hospital day the temperature fell to not more than 100 F. (37.8 C.) and the patient seemed to be over his disease. However, on the eleventh hospital day he began to complain of sore throat, the temperature began to rise, and a repeat white blood cell count was 21,050, with 57 per cent lymphocytes, 4 per cent monocytes and 39 per cent neutrophils. Prior to this time the heterophile antibody reaction had remained negative, but a repeat test done on that day was positive, in a 1:320 dilution. The sore throat became progressively severer. Both tonsils enlarged rapidly and were covered with a gray pseudomembrane. A smear for Vincent's organisms was negative. He

complained bitterly of extremely sore throat, and swallowing or talking was very difficult. The temperature gradually rose so that on the third day following the onset of the tonsillitis, it had reached 104 F. (40 C.). At this time 20,000 Oxford units of penicillin were given intramuscularly every three hours. Within twelve hours the throat appeared much better, and the patient did not complain of so much pain. The temperature fell by crisis and in less than twenty-four hours it was not above 100 F. (37.8 C.). The throat very rapidly improved so that within three days it appeared normal. Penicillin was continued in treating the tonsillitis for three days for a total of 460,000 units. The patient's convalescence was slow. He was discharged to full duty thirty-two days after his admission.

CASE 2.—A white officer, 24 years old, was admitted on March 13, 1945, complaining of enlarged lymph nodes in the left side of his neck which had been present for five days. On admission this patient did not appear ill, but a heterophile antibody test done the day prior to admission elicited a positive reaction in a dilution of 1:320. The white blood cell count was 6,850, with 36 per cent

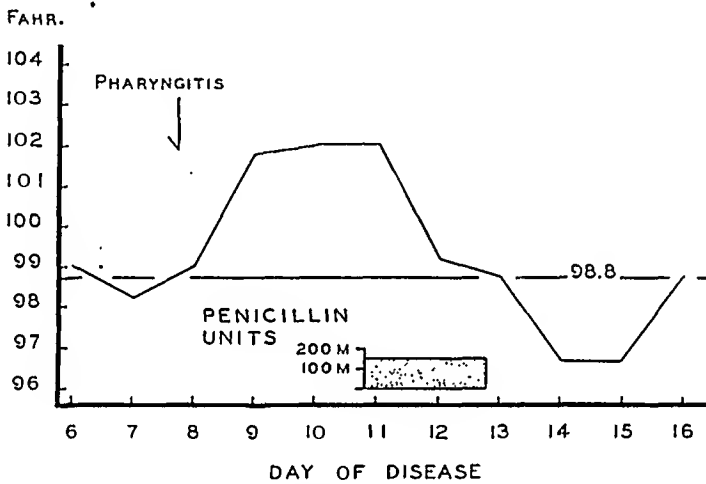


Fig. 2 (case 2).—The onset is illustrative of a severe ulcerative pharyngitis as a complication of infectious mononucleosis (anginose type) and the response to penicillin.

neutrophils and 64 per cent lymphocytes. The blood smear revealed abnormal lymphocytes. The physical examination showed nothing abnormal except for slightly enlarged lymph nodes in the submental area and in the left anterior cervical region. The spleen was not palpable. The patient did not complain of sore throat, and the throat appeared normal on examination. However, on the second hospital day he complained of sore throat, but there was no enlargement of the tonsils. By the third day the temperature had reached 101.4 F. (38.5 C.), and the sore throat had become much worse. Examination revealed an ulcerative pharyngitis. In the meantime the lymph nodes of the neck became considerably larger, and there was slight enlargement of the axillary lymph nodes. On the fifth hospital day, which was the tenth day of his illness, the temperature was elevated to 102 F. (38.9 C.), and the patient was acutely ill. Twenty thousand units of penicillin were given every three hours intramuscularly for a total of 320,000 units. The temperature very promptly subsided and within twelve hours had fallen to normal, with noticeable improvement in the throat. The subjective improvement in the throat was more pronounced than the physical appearance,

but the pharyngitis rapidly subsided and the patient made an uneventful recovery. He was discharged from the hospital fourteen days after admission.

CASE 3.—An officer, 24 years old, was admitted to the hospital on April 3, 1945, on the third day of his illness. The onset was accompanied by chills, fever, malaise and generalized aching pains. He also noticed soreness and bleeding of the gums, and the following day he reported to the dental clinic, where a diagnosis of Vincent's gingivitis was made, and penicillin mouth washes were prescribed. On the third day he awakened with high fever, all his symptoms had become worse, and he had a very sore throat. The past personal and familial history was irrelevant.

On admission his temperature was 103 F. (39.4 C.). He appeared very ill, and talking and swallowing were painful. Both gums were swollen, bled easily on touching and showed numerous small white ulcers. The tonsils had been enucleated but the tonsillar fossae were studded with lesions similar to those on the gums. The pharynx was acutely inflamed but showed no ulceration. The ears, eyes and nose were normal. The lymph nodes in both anterior cervical triangles were enlarged and were slightly tender. The lungs were normal. The cardiovascular system was normal; the pulse rate was 110, and the blood pressure was 115 systolic and 60 diastolic. There was no tenderness or enlargement of the abdominal viscera on palpation. The urogenital organs were normal. Except in the neck, the lymph nodes were not enlarged enough to be felt. Ninety grains (6 Gm.) of sulfadiazine with 180 grains (12 Gm.) of sodium bicarbonate were given during the first eight hours, followed by 15 grains (1 Gm.) of sulfadiazine and 37.5 grains (2.5 Gm.) of sodium bicarbonate every four hours. The penicillin mouth washes which had been started on the day prior to admission were continued. Although the diagnosis of Vincent's infection had already been made, a throat culture revealed nonhemolytic streptococci and pneumococci as the predominating organisms. No diphtheria bacilli were seen on smear or grown on culture. The white blood cell count was 10,700, with 67 per cent neutrophils, 31 per cent lymphocytes and 2 per cent eosinophils. No abnormal lymphocytes were seen. The urine, hemoglobin and red blood cell count were normal.

The day after admission the temperature was 103.4 F. (39.6 C.), and the throat and mouth lesions were worse. Use of sulfadiazine was stopped and penicillin begun, 20,000 units intramuscularly every three hours. The white blood cell count had dropped to 6,500, with 80 per cent neutrophils and 20 per cent lymphocytes. The heterophile antibody reaction was negative. The temperature remained elevated during the first twenty-four hours after the penicillin was begun and, although the patient complained less of the sore throat, there was no apparent change in the appearance of the gums or throat. Penicillin was continued, and after forty-eight hours the temperature had dropped to 100.4 F. (38 C.), with considerable improvement in the appearance of the throat lesions but with no noticeable change in the gums. Penicillin intramuscularly was continued until he had had 460,000 units over a period of sixty-nine hours. At the end of this time the temperature ranged from 98.6 F. to 100 F. (37 C. to 37.8 C.). The white blood cell count was 6,750, with 52 per cent neutrophils, 6 per cent eosinophils and 42 per cent lymphocytes. Although infectious mononucleosis had been suspected, this slight increase in the lymphocytes was the first laboratory evidence suggestive of this diagnosis. Four days later (the eighth hospital day) the heterophile antibody reaction became positive in a dilution of 1:80, and six days later it became negative. There were no diagnostic observations of the blood picture during the short time the heterophile antibody test elicited a positive reaction.

However, after the reaction had become negative, the blood picture became typical of infectious mononucleosis.

The gingivitis continued to cause trouble for six days after the course of penicillin had been completed, in spite of the continuous use of the penicillin mouth washes. Although there had been healing of the ulcers, the gums remained edematous, bled easily and healed slowly. The patient had no fever during this time. At no time did lymph nodes become palpable except in the neck, and the spleen was never felt. He returned to duty fifteen days after admission.

COMMENT

During World War II, military medicine afforded opportunity for one to determine effectively the incidence of diseases which are peculiar to the group of military age. In this respect (excluding battle casualties) military hospitals would compare with infirmaries serving college students, since the age groups are approximately the same. Contratto² reports that infectious mononucleosis accounted for 1.5 per cent of 12,601 medical admissions. In this study infectious mononucleosis was present in 0.31 per cent of 10,000 patients admitted consecutively to the medical and surgical services. There was an insignificant number of battle casualties among those admitted to the surgical services. The ratio of the patients admitted to the medical services and those to the surgical was not actually determined, but 10 samples of 100 patients each, spread equally over a twenty-four-month period, showed the proportion to be 72 per cent admitted to the medical and 28 per cent to the surgical services. The corrected incidence of infectious mononucleosis was 0.43 per cent of 10,000 patients admitted to the medical services. This is considerably lower than the incidence given by Contratto, and although military hospitals are occupied almost exclusively by males, a correction for the sex ratio would still not elevate the percentage more than twofold. As was brought out by Contratto, the percentage of patients admitted for infectious mononucleosis in a hospital concerned chiefly with the treatment of young adults is much higher than in a general hospital, which cares for patients of all ages. He reported 61 patients with infectious mononucleosis among 16,907 patients admitted to the medical services of Peter Bent Brigham Hospital in a period of seven years and nine months.

The pseudomembrane covering the ulcerative pharyngeal or tonsillar lesions in infectious mononucleosis is sometimes mistaken for diphtheria. When it is present the throat smears are often positive for Vincent's organisms. It is not uncommonly seen in infectious mononucleosis, and almost every report on the clinical aspect of this disease contains some reference to it. The report of Press and his colleagues³ is unique in this respect, since they state that they did not observe a single case of Vincent's angina in their large series of cases of infectious mononucleosis. In this series of cases, Vincent's organisms were present in 10 (52

per cent) of the 19 cases of infectious mononucleosis which were complicated by pharyngeal or tonsillar lesions. Considering this relatively high incidence of Vincent's angina as a complication of infectious mononucleosis, it was expected that a review of the case histories of primary Vincent's angina would reveal a high incidence of cases containing evidence that infectious mononucleosis may have been the proper diagnosis. This did not prove to be true. Only 2 such cases were found among the 33 cases of Vincent's angina which were considered in this study. This amounted to 6 per cent and was lower than the anticipated level. Eight per cent of the clinical records of 175 cases of acute tonsillitis revealed considerable evidence that infectious mononucleosis should have been the proper diagnosis. Eight per cent of the cases of infectious hepatitis contained similar evidence suggestive of an improper diagnosis. Many reports on infectious mononucleosis mention how frequently this disease may be missed because it may simulate these conditions. To my knowledge, these are the first statistical studies in this respect, and serve only to emphasize what has been long known but too frequently forgotten.

Sore throat is so frequently seen in infectious mononucleosis that in the absence of acute ulcerative pharyngitis or acute tonsillitis, it must be considered as one of the symptoms of infectious mononucleosis. The cause is obscure and without visible local pathologic conditions it is not possible to say that this is due to secondary infection. Ulcerative pharyngitis and acute tonsillitis do not fall in this same category. It is easy to incriminate the tonsillar lesions as being part of the disease entity when the lymph nodes throughout the body may be generally involved. However, the ulcerative lesions may occur on the soft palate, the tonsillar pillars or the posterior pharyngeal wall and often do not arise from involved lymphoid tissue. Bernstein,¹¹ in his excellent review, stated his belief that ulcerative pharyngitis and acute tonsillitis were complications rather than part of the disease itself, and that these inflammatory lesions are not different from similar complications occurring in such conditions as the leukemias or agranulocytosis.

Why these two particular complications should occur so frequently in infectious mononucleosis has not been determined. Undoubtedly, there must be a lowered resistance of the patient to virulent organisms. There seems to be little relation between the onset of these complications and the white blood cell count. In some cases showing severe throat lesions the neutrophile count may be low, normal or elevated. A relative or absolute lymphocytosis with a corresponding granulocytopenia usually occurs at some time in infectious mononucleosis, and it would seem that the granulocytopenia might be responsible for the lowered resistance of the host. While this may be true in some cases, granu-

11. Bernstein, A.: Infectious Mononucleosis, *Medicine* 19:85-159 (Feb.) 1940.

locytopenia frequently does not occur until perhaps long after the throat complication has subsided. Read and Helwig⁶ believe that granulocytopenia, anemia, or thrombopenia occurring in infectious mononucleosis is the result of a focal infectious granulomatous process in the bone marrow with a secondary depression of hemopoietic activity. Others regard this pathologic process as a simple heteroplastic infiltration of the bone marrow. In either case, the absence of leukocytosis in the tonsillitis or membranous pharyngitis complicating infectious mononucleosis might well be accounted for by an inability of the hemopoietic system to respond rather than by a lack of stimulation and would not, therefore, be a valid argument that these particular throat lesions are part of the disease entity. Menkin¹² has reported a substance found in inflammatory exudates and hemolyzed blood serum which he has called necrosin. When necrosin is injected into test animals, an inflammatory reaction occurs at the site of injection which is accompanied by systemic changes manifested by high fever, diarrhea, damage to the liver and granulocytopenia. Although a granulocytopenia does not always occur in infectious mononucleosis, it is possible that necrosin or some similar substance is liberated which suppresses the normal neutrophile response to a secondary invasion of the host. In general, however, virus infections (and some bacillary infections) cause very little neutrophile response, and ulcerative pharyngitis or tonsillitis is a not frequently occurring complication of such diseases.

The throat lesions complicating infectious mononucleosis were found to occur on an average of seven days after the onset of the disease. Almost invariably these lesions were accompanied with fever, which in some cases was high. In many of the cases the fever was low during the first few days following admission and became elevated if a throat complication developed. In other cases the initial phase of the disease may have been very stormy and the patient might have chills and high fever for two or more days; this would subside with apparent recovery from the disease for a few days. However, after this brief interlude of well-being the throat complications developed and were accompanied with another rise in fever, which in some cases was higher than the fever occurring during the initial phase of the disease. When this occurred, the patient was usually more acutely ill and uncomfortable than during the period of stormy onset. The latter type of fever curve in infectious mononucleosis occurred in 7 of the 31 cases and was similar to the "saddleback" fever which occurs in other diseases. Considerable variation in the degree and type of the fever curve in infectious mononucleosis

12. Menkin, V.: Further Studies on the Leukocytosis-Promoting Factor and on Necrosin in Inflammatory Exudates, *Am. J. M. Sc.* **208**:290-297 (Sept.) 1944.

has been known for some time. Mills¹³ described "saddleback" fever occurring in this disease in 1932. Relapses and recrudescences may occur and could easily explain this type of fever curve, but this clinical feature, which occurred in 23 per cent of this series of cases, has been given very little attention in previous studies of the disease. Contratto mentions this type of fever and states, "The amount of fever and its duration did not seem necessarily related to either the sore throat or the blood count." I agree entirely with that part of the statement in regard to the blood count but in none of the cases in this series in which there was saddleback fever did the secondary elevation of fever occur unless tonsillitis or pharyngitis was present at the same time. Since relapses and recrudescences occur, it would be difficult to prove that the secondary rise in fever was caused by the complicating throat infection. Especially would this seem true when there was no elevation of the white blood cell count.

However, there remains one very strong argument in favor of this contradictory conception, i. e., in 3 of the 4 cases in which penicillin was used to treat the pharyngitis or tonsillitis occurring in infectious mononucleosis there was a dramatic response to this therapy in every respect. While it seems well established that penicillin is of no benefit when used to treat infectious mononucleosis, the only explanation for its dramatic effect in these cases is that it cured a complicating infectious process caused by organisms which are susceptible to penicillin. The 1 exceptional case which did not respond so favorably to penicillin was a case in which there was a very severe Vincent's infection of the gingivae and pharyngeal wall. The temperature in this case fell slowly from 103.2 F. (39.5 C.) to normal within seventy-two hours, and although the patient did feel better, the gingivitis remained troublesome several days after the temperature was normal and in spite of daily penicillin mouth washes. The pharyngeal lesions healed rapidly after penicillin was started. Pearce and McDonald¹⁴ reported the favorable response of fusospirochetosis treated with penicillin. These authors contrasted the results obtained with various dosages. They obtained negative smears in twenty-four hours with complete healing in ninety-six hours in 95 per cent of the cases. using penicillin in doses of 10,000 units every two hours until 100,000 units had been given; these patients also received dental care and oxygenating mouth washes. Not so striking were the results when penicillin was used in the more conventional dosage of 20,000 units every

13. Mills, J.: Glandular Fever, Roy. Berkshire Hosp. Rep., 1932, p. 66; cited by Bernstein.¹¹

14. Pearce, W. F., and McDonald, J. B.: Treatment of Ambulatory Patients with Penicillin Sodium: Preliminary Studies of Fusospirochetosis, J. A. M. A. **128**:342-344 (June 2) 1945.

three hours, which was the dosage used in this series of cases. In that group only 53 per cent of the patients were cured in twenty-four hours. The throat smears were negative for Vincent's organisms in the 3 cases in which there was a good response to penicillin.

The response of the throat complications to sulfadiazine when used in adequate doses was considerably less impressive. Fusospirochetosis does not respond well to sulfadiazine, and although streptococcus, staphylococcus, and pneumococcus throat infections respond to the sulfonamide drugs it is seldom that the degree of response is as great as that seen when penicillin is used.

In many patients who are acutely ill with infectious mononucleosis sore throat or tonsillitis never develops. However, the conception that these particular conditions are a part of this clinical entity has become well established, both in regard to the frequency of their occurrence and their causal relationship. Add to this the fact that penicillin is of no benefit in the treatment of infectious mononucleosis per se, and the result will be the failure to use penicillin in the treatment of any phase of the disease. Although the patients treated with penicillin are too few to warrant a dogmatic statement proclaiming its unquestionable value in treating these severe conditions complicating infectious mononucleosis, the results do justify further trial of penicillin in the treatment of infectious mononucleosis, not to treat the disease in all its many forms, but specifically for the throat lesions which not uncommonly are more disabling than any other phase of the disease.

SUMMARY

1. In a study of the case histories of acute tonsillitis, Vincent's angina and infectious hepatitis, evidence was found in 6 to 8 per cent of the cases which indicated that infectious mononucleosis should, perhaps, have been the proper diagnosis.

2. The causal relation of the severe throat conditions in infectious mononucleosis is discussed.

3. Evidence is presented which warrants the further use of penicillin in treating the severe throat lesions accompanying infectious mononucleosis.

NOTE.—After the foregoing paper was accepted for publication French reported a study of 54 cases of infectious mononucleosis (French, P. K.: Infectious Mononucleosis, *Air Surgeon's Bull.* 7:414 [Nov.] 1945) and stated that the treatment is purely symptomatic: "Sulfadiazine and penicillin are useful for secondary infections but of no value in mononucleosis itself."

PLASMA QUINACRINE CONCENTRATION AS A FUNCTION OF DOSAGE AND ENVIRONMENT

A Joint Report of the Armored Medical Research Laboratory, Fort Knox, Ky.,
and the Commission on Tropical Diseases, Army Epidemiological Board,
Preventive Medicine Service, Office of The Surgeon General,
United States Army

INTRODUCTION

THIS report deals with a study¹ carried out at the Armored Medical Research Laboratory as a part of the program of the Commission on Tropical Diseases of the Surgeon General's Office for the investigation of quinacrine hydrochloride (atabrine) therapy. The primary purposes of the study were: (1) to determine the plasma quinacrine levels in large groups of healthy young men on several suppressive regimens of the drug, (2) to determine the influence of a simulated jungle climate on plasma quinacrine concentrations, (3) to determine the effect of quinacrine on acclimatization and performance of men in humid heat and (4) to determine the plasma concentrations for therapeutic levels of quinacrine intake and relate these concentrations to the plasma concentrations of the same subjects on suppressive regimens. It was anticipated that such information, together with that which was already available,² would facilitate the designing of regimens of quinacrine therapy suitable for application to large groups of persons.

The choice of the concentration of quinacrine in the plasma instead of in the whole blood as an index of the effective concentration of the drug has been discussed elsewhere.² Briefly the basis is the following: Protein and other cellular constituents have a great affinity for the drug.

The following persons collaborated in this investigation: from the staff of the Armored Medical Research Laboratory—Major Norton Nelson and Lieutenant Colonel Frederick S. Brackett, Sanitary Corps, Army of the United States, and Major William F. Ashe, Major Ludwig W. Eichna and Major William B. Bean, Medical Corps, Army of the United States; specially attached through the Office of the Surgeon General—First Lieutenant E. D. Connor, Lieutenant Colonel A. C. McGuinness, Captain Morris Rosenfeld, Captain L. D. Rosenman and Captain Maurice Wince, Medical Corps, Army of the United States, and Captain R. G. Gould, Sanitary Corps, Army of the United States; representing the Commission on Tropical Diseases, Army Epidemiological Board—James A. Shannon, M.D.

1. Investigation of the Effects of Activity and Environment on Atabrine Therapy, Armored Medical Research Laboratory, Final Report on Project No. 18, Dec. 23, 1943.

2. Shannon, J. A.; Earle, D. P., Jr.; Brodie, B. B.; Taggart, J. V., and Berliner, R. W.: J. Pharmacol. & Exper. Therap. **81**:307, 1944.

In the plasma phase approximately 90 per cent of the quinacrine is reversibly adsorbed by the plasma protein. At normal tissue p_H quinacrine is two to six times as concentrated in red cells as in plasma and one hundred to two hundred times as concentrated in leukocytes as in plasma. Thus, variations in leukocyte count alone may be responsible for large changes in the concentration of quinacrine in whole blood. The most desirable index of the effective concentration of quinacrine would be its concentration in plasma water, since this concentration reflects the distribution of the drug in the various tissues and organs of the body. However, the difficulty of this measurement necessitates the choice, for most purposes, of the total plasma concentration. This can be expected to be a reliable index if the plasma protein concentration is not abnormal and if the distribution ratio from plasma protein to plasma water is stable from time to time and from man to man. The great affinity of protein for quinacrine is perhaps the dominant characteristic in determining the metabolism and distribution of the drug. The body can be considered a quinacrine reservoir of considerable capacity.

Since the plasma quinacrine levels of different men on the same dosage regimen differ widely, it is apparent that the general pattern can be most easily detected and followed in the plasma level of a group. Once the basic characteristics of the pattern are apparent, the extent and frequency of individual deviations from the group pattern can be considered. A second consideration which suggests a useful approach to the analysis of quinacrine metabolism is the characteristic distinction between the changes in plasma level during the twenty-four hours after ingestion of quinacrine and the changes during the days or weeks following a dose. The typical response to ingestion of a single dose of the drug is a rapid rise in plasma quinacrine concentration followed by an initial rapid decrease in concentration which subsequently slows until by twenty to twenty-four hours after ingestion the rate of decrease of plasma quinacrine has decreased to a uniform rate which continues until the plasma is cleared of the drug. The rapid changes in plasma level occurring after ingestion of the quinacrine probably reflect the rapid rate of absorption of the drug and its subsequent distribution throughout the fluids and tissues of the body. The slower changes probably arise from its degradation and excretion. The levels found twenty-four hours after the last dose of the drug, or which would be obtained earlier if absorption and distribution were complete, are considered as "underlying levels"; the concentrations actually determined during the twenty to twenty-four hours after administration are considered as "transient levels," which can be thought of as superimposed on the fictive "underlying level" during this early interval. These concepts have partly dictated the order of presentation of our results, which have been divided into six sections. These are:

I. Plasma quinacrine concentration following single oral doses. This section considers the transient (up to twenty-four hours) changes in plasma quinacrine from a single dose and relates these changes to the previous intake of the drug and to the amount of the dose ingested.

II. Plasma concentrations resulting from several dosage regimens. This section is concerned with the slower trends—over days and weeks—in the plasma quinacrine concentration from several dosage regimens. The gradual build-up of plasma concentration to a steady state, or equilibrium level, is shown for two schedules having a uniform rate of intake throughout. The possibility of more rapidly attaining the desired equilibrium concentrations is considered with respect to three different “booster” or “priming” schedules. Finally, plasma levels are presented for a therapeutic regimen of quinacrine following a suppressive regimen.

III. Plasma concentrations after cessation of dosage and after interruption of dosage. This section considers the rate of disappearance of quinacrine from the plasma when the intake is stopped after attainment of equilibrium concentrations and the rate of increase of plasma concentration after resumption of dosage after interruptions of one week and two weeks.

IV. Individual variation of plasma concentration and prediction of concentration. In this section the spread of individual values within groups on the same schedule are discussed from the point of view of the statistical probability that a given regimen will produce a predetermined concentration of quinacrine in the plasma of a single individual. In addition, a basic generalization is presented which describes the group mean plasma concentration for all the dosage regimens studied.

V. The influence of simulated jungle climate on plasma quinacrine concentration. This section considers whether the plasma quinacrine concentrations in profusely sweating men in humid heat differ from the levels attained by men in a temperate climate and whether intake of the drug modifies the work performance in humid heat.

VI. The toxicity of quinacrine.

PROCEDURE

Chemical Method.—Plasma quinacrine was determined by the method of Brodie and Udenfriend.³ The method is based on the measurement of the intensity of fluorescence, which, in turn, is proportional to the concentration of quinacrine. Preliminary removal of interfering fluorescent materials is accomplished in two steps: (1) by extraction

3. Brodie, B. B., and Udenfriend, S.: *J. Biol. Chem.* **151**:299, 1943.

of the organic base, quinacrine, from alkalized plasma by shaking with ethylene chloride (1, 2-dichloroethane) and (2) transfer of the quinacrine from the ethylene chloride to concentrated lactic acid, again by shaking. The fluorescence is measured directly in the lactic acid solution with a photoelectric fluorometer. Minor modifications facilitated the handling of large numbers of specimens.

Preparation of Specimens.—Since the concentration of quinacrine in the leukocytes is very much higher than in the plasma and since leukocytes begin to disintegrate quickly after blood is drawn, it is imperative to separate the plasma soon after drawing the blood in order to avoid contamination of the plasma by quinacrine from the leukocytes. It is necessary to free the plasma of all leukocytes by adequate centrifugation. These conditions can be fulfilled only when the blood stands less than fifteen minutes before centrifugation. Twenty-five to 30 cc. of blood was collected in a 30 cc. syringe containing 6 drops of saturated solution of potassium oxalate. After mixing, the blood was transferred to a tube and centrifugation begun within fifteen minutes of the withdrawal of any blood sample. After centrifugation at 2,000 revolutions per minute for fifteen minutes the plasma was pipetted off and then recentrifuged for an additional hour. This procedure minimized the possibility of accidental contamination by leukocytes.

Reliability of Analytic Results.—It is believed that the management of the bleeding and the preparation of plasma were sufficiently controlled to meet all requirements of the present study. Accidental contamination by leukocytes or extraneous fluorescent materials presented no problem. In several thousand analyses performed there were only 8 or 10 instances in which contamination was demonstrated. A decided advantage was gained by the uniformity of handling which obtains when analyses are carried out on a large scale.

Most of the plasma quinacrine levels encountered were at the lower limits of suitability of the technic. The limiting factors in the procedure are: (1) extraneous nonfluorescent light—this gave deflections equivalent to 8 to 12 micrograms of quinacrine per liter; (2) extraneous fluorescence (irreducible blank in reagents)—amounting to another 8 to 12 micrograms per liter; (3) instrumental limitations, imposed by the sensitivity of the instrument (always used at maximum sensitivity), stability of the instrument, stability of the light source and the residual inequality of the cuvettes. The net effect of these factors was such that the reproducibility of measurement in the range up to 30 micrograms per liter was generally within plus-minus 2 micrograms. The absolute value of the analytic results was generally reliable enough to keep the over-all precision within this range of plus-minus 2 micrograms. In a

few runs the calibration procedure undoubtedly led to considerably greater absolute errors.⁴

Subjects.—The subjects in this study were healthy young adult enlisted men in the army. Their age range was 18 to 37 years with approximately one half between 18 and 20 years, one quarter between 20 and 25 years and one quarter over 25 years. Except for the group living in the humid heat their living conditions, clothing, duties and messing were those of any other soldier. Their medical attention was more solicitous than was that of their confrères in order that toxic manifestations of the drug might not be overlooked. This was done without causing the subjects to focus on their part in the problem. This study was carried out from early August to mid-November 1943.

Group Composition.—In order that the various aspects of the metabolism of quinacrine might be studied several groups of men were placed on different dosages and schedules of intake of the drug. Since these groups will be referred to repeatedly, either singly or in combination, throughout this report, it seemed desirable to describe at the outset each group with regard to its purpose, dosage schedule, composition and handling. This is done in detail in table 1.

Group C (C1, C2 and C3).—The C groups served two purposes: (1) to determine the plasma quinacrine absorption curves during the twenty-four to forty-eight hours after the ingestion of single doses of quinacrine at different plasma concentrations of the drug and (2) to determine the effect of larger initial ("priming") doses on the time required to reach a predetermined level of plasma quinacrine. These groups received higher initial doses (0.2 Gm. to 0.3 Gm. per day) followed after varying periods by a maintenance dosage regimen (0.1 Gm. per day). The individual subgroups were small: 4, 4 and 6 men respectively. These men had finished basic and battle training. They performed company duty and lived in regular army barracks.

ARTC Groups (Company B, Sections 1 and 2, Company C, Sections 1 and 2).—These groups, obtained from the Armored Replacement Training Center, served to determine the equilibrium levels of plasma quinacrine attained by large groups of men placed on two constant suppressive dosage regimens of 0.4 Gm. and 0.6 Gm. of quinacrine per week (tables 1 and 2). Because of the dosage and bleeding schedules and the large number of blood samples requiring analysis it was necessary during the first nine weeks of the eleven weeks of suppressive

4. Analytic difficulties with the specimens taken on the following dates gave basis for questioning the reliability of the values obtained: jungle groups, Sept. 11, 1943 (H₂SO₄ only), Sept. 13, 1943, Sept. 20, 1943 and Oct. 27, 1943; Company B, Section 1, Oct. 15, 1943, and Oct. 18, 1943; Company B, Section 2, Oct. 27, 1943, and Company C, Section 2, Sept. 18, 1943.

therapy to modify the two dosage regimens from the standard schedules of the Surgeon General's Office.⁵ During the last two weeks the regimens were in strict accordance with the schedules of the Surgeon General's Office. During the ensuing twelfth week the drug was withheld from half of the men in order that the curve of disappearance of plasma quinacrine ("die-away") with discontinuance of the drug might be determined. The other half of the men were placed on a modified

		Weeks															
Group Code	No. of Men	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
C1	(4 men)	0.2 Gm./day 17 days out of 19			← 0.6 Gm./wk. (0.1 Gm./day x 6) →												
C2	(4 men)	0.2 Gm./day 17 days out of 19			← 0.6 Gm./wk. (0.1 Gm./day x 6) →												
C3	(6 men)	0.3 Gm./day 6 days	0.2 Gm./day 6 days	← 0.6 Gm./wk. (0.1 Gm./day x 6) →													
ARTC Groups*	Co. B Sect. 1 (50 men)	← 0.4 Gm./wk. (modified SGO schedule)* →										0.4 Gm./wk. (SGO schedule)*		2.1 [†] Gm./wk.			
	Co. C Sect. 1 (50 men)	← 0.4 Gm./wk. (modified SGO schedule)* →										0.4 Gm./wk. (SGO schedule)*		No drug			
	Co. B Sect. 2 (50 men)	← 0.6 Gm./wk. (modified SGO schedule)* →										0.6 Gm./wk. (SGO schedule)*		2.1 [†] Gm./wk.			
	Co. C Sect. 2 (50 men)	← 0.6 Gm./wk. (modified SGO schedule)* →										0.6 Gm./wk. (SGO schedule)*		No drug			
Jungle Group	A (15 men)	1.2 Gm./wk.	← 0.6 Gm./wk. (0.1 Gm./day x 6) →					← 0.6 Gm./wk. (0.1 Gm./day x 6) →					No drug	X	0.6 Gm./wk.		
		0.2 Gm./day 6 days	Jungle hot room					← Summer out-of-doors →							Y	No drug	
	B (15 men)	1.2 Gm./wk.	← 0.6 Gm./wk. (0.1 Gm./day x 6) →					← 0.6 Gm./wk. (0.1 Gm./day x 6) →					No drug	Y		0.6 Gm./wk.	
		0.2 Gm./day 6 days	← Summer out-of-doors →					Jungle hot room							X	0.6 Gm./wk.	

* Detailed breakdown of daily dosage and relation of bleeding to dosage is given in table 2.

† Therapeutic dosage, details of which are given in table 2.

therapeutic dosage⁵ of quinacrine. This permitted the determination of the therapeutic plasma quinacrine levels and their relationship to suppressive levels in the same men. At the onset of the study 200 men, divided in four sections of 50 men each, comprised this group; at the end 168 men remained; 32 men were lost for varying reasons not associated with the experiment. All men in the ARTC group were in basic training and throughout the study lived the life of such soldiers in all respects.

5. The Drug Treatment of Malaria, Suppressive and Clinical, Circular Letter No. 153, Office of the Surgeon General, War Department, J.A.M.A. 123:205 (Sept. 25) 1943.

Jungle Groups A and B.—These groups served to determine the effect of humid (jungle) heat, with its profuse sweating, on the level of plasma quinacrine attained on a standard suppressive regimen and, incidentally, the effect of quinacrine on the ability of men to acclimatize and work in humid heat. Since the dosage during the first week was twice the maintenance dosage, the effect of a short "priming" schedule on the time to reach maintenance levels was also obtained. Moreover, the discontinuance of the drug after eleven weeks of suppressive therapy with its resumption after one and two weeks permitted the study of the effect of interruption of dosage.

TABLE 2.—*Dosage and Sampling Schedules for Companies B and C, Fifth Battalion, ARTC (Doses in Grams)*

	Weeks One Through Nine						
	Sun.	Mon.	Tues.	Wed.	Thur.	Fri.	Sat.
Co. B Section 1	No drug	$H_2 \& H_2 + .5$ 0.10	0.10	0.05	0.05	H_1 0.05	0.05
Co. B Section 2	No drug	0.10	0.10	$H_2 \& H_2 + .5$ 0.10	No drug	H_1 0.10	0.20
Co. C Section 1	No drug	0.05	$H_2 \& H_2 + .5$ 0.10	0.10	0.05	0.05	H_1 0.05
Co. C Section 2	No drug	0.10	0.10	0.10	$H_2 \& H_2 + .5$ 0.10	No drug	H_1 0.20
	Weeks Ten and Eleven						
	Sun.	Mon.	Tues.	Wed.	Thur.	Fri.	Sat.
Co. B Section 1	0.05	H_2 0.10	H_1 0.05	0.05	0.05	0.05	0.05
Co. B Section 2	0.10	0.10	0.10	H_2 0.10	No drug	H_1 0.10	0.10
Co. C Section 1	0.05	0.05	H_2 0.10	H_1 0.05	0.05	0.05	0.05
Co. C Section 2	0.10	0.10	0.10	0.10	H_2 0.10	No drug	H_1 0.10
	Week Twelve						
	Sun.	Mon.	Tues.	Wed.	Thur.	Fri.	Sat.
Co. B both sections	0.50	0.30	0.30	0.30	H_a 0.30	H_b 0.30	H_c 0.10
Co. C both sections	No drug	H_x No drug	No drug	H_y No drug	No drug	No drug	H_z No drug

Blood sampling schedule: H_1 and $H_2 = 11:30$ a.m.; $H_{2+.5} = 4:30$ p.m.; $H_{a,b,c}$ = samples during therapeutic dosage; $H_{x,y,z}$ = samples during die-away.

Thirty men who had recently finished basic and battle training were divided into two equal and comparable groups A and B. While one group was living and working in the humid (jungle) heat of the hot room the other group was living and working in the summer out-of-doors of the post. Both groups received exactly the same dosage of quinacrine according to the same schedule; 1.2 Gm. per week for the first week and 0.6 Gm. per week for the next ten weeks. After seven weeks the two groups were switched with regard to the environment alone; the hot room group moving out-of-doors and the out-of-doors group going into the hot room.

Control of Dosage.—In order to insure complete control of drug intake, the quinacrine hydrochloride (0.1 Gm. tablets) was always given under the actual supervision of personnel from the laboratory.

Bleeding Schedule.—The detailed sampling plans are given in their corresponding sections. The design for the regularly scheduled dosage patterns was to secure the minimum levels of the week from bloods drawn twenty-four or more hours after the last dose and the maximum level of the week from bloods drawn five hours after the last or largest dose of the week. The sample for the minimum level is designated as H_1 , the level before the last or largest dose of the week as H_2 and the maximum level, drawn five hours after the H_2 sample, as H_{2+5} .

Expression of Results.—Plasma concentrations are expressed as micrograms of quinacrine (base) per liter of plasma. The expression of the central tendency chosen to represent group results was the geometric mean, written "MEAN_G." The use of the geometric mean rather than the median or the arithmetic mean was based on the distribution of the data, which in all cases showed better fit with a logarithmic probability curve than with an arithmetic probability curve. This is more extensively considered in section IV.

I. PLASMA QUINACRINE CONCENTRATION FOLLOWING SINGLE ORAL DOSES

The course of rise and fall of plasma quinacrine in the hours immediately following a single oral dose of the drug was followed after the first dose and at several periods during a regular schedule of quinacrine intake. It was hoped in this way that a more detailed picture might be gained of quinacrine levels in the larger groups where sampling was possible less frequently.

Procedure.—The subjects of groups C1, C2 and C3 served for this study. Details of their dosage regimens are indicated in table 1. The absorption curves were determined after single oral doses of 0.2 Gm. (groups C1 and C2) and 0.3 Gm. (group C3) at several stages during the course of the dosage schedules indicated in table 1, i. e., at various levels of plasma quinacrine.

Blood samples (30 cc.) for determination of absorption curves were taken before the drug was given and two, four, six, eight, twelve, twenty-four and, at times, forty-eight hours after the dose. In addition, samples were obtained regularly three times weekly in accordance with the bleeding plan described in the introduction.

Results.—The rise and fall of the plasma quinacrine concentration immediately following a single oral dose of 0.2 Gm. is shown in chart 1. The lowest curve represents the response to the first dose of quinacrine. The rapid rise in plasma level in two hours indicates rapid absorption of the drug. The level is maintained until the fourth hour and then gradually declines. At twenty-four hours there is still an appreciable amount of quinacrine present, suggesting that another dose taken at this

time would produce a superposition of its response curve on the starting level. That this is the case is indicated by the second curve from the bottom of chart 1, which charts the plasma levels after the fourth daily dose of 0.2 Gm. Here the starting level of 9 micrograms per liter results from the accumulation of the preceding three doses. This curve again indicates a rapid rise in two hours, but now the peak level appears to persist for nearly eight hours before falling. The twenty-four hour level again indicates that a net daily gain in plasma level is still occurring at this stage of a daily intake of 0.2 Gm. per day. The uppermost curve, which presents the results after the sixteenth daily dose of 0.2 Gm.,

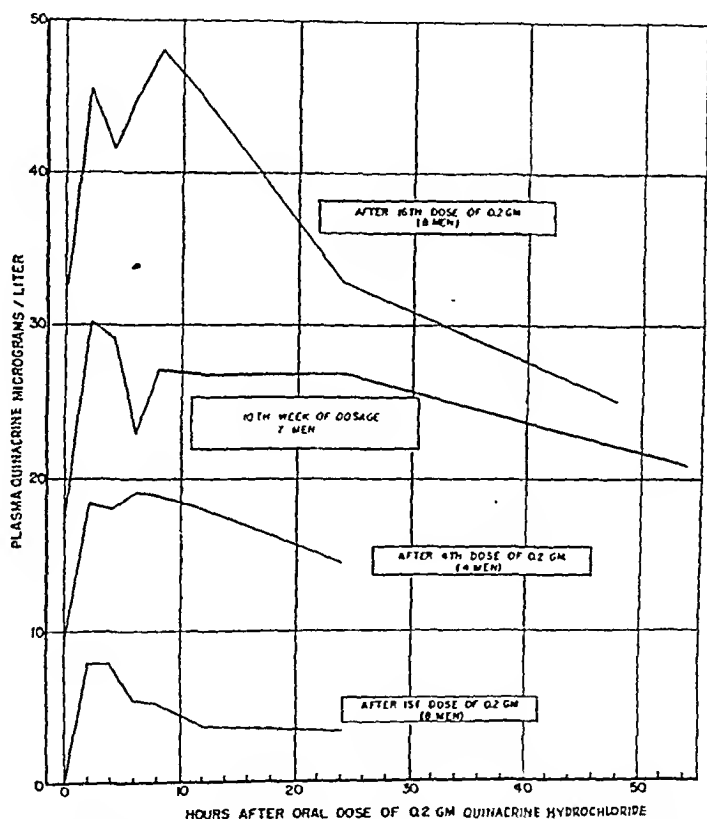


Chart 1.—Postabsorption curves of plasma quinacrine concentration following 0.2 Gm. dose.

shows, first, that a plasma accumulation of better than 30 micrograms per liter has resulted from the previous fifteen doses and, second, that at this high concentration the rate of loss from the plasma has so increased that in twenty-four hours the plasma level has fallen to its pre-dosage level. This suggests that a state of equilibrium has been attained for this rate of intake, that is, that rate of loss from the plasma over twenty-four hours is now equal to the daily intake of the drug. After seventeen daily doses of 0.2 Gm. the dose was reduced to 0.1 Gm. per day, six days a week. The third curve from the bottom of chart 1 demonstrates the response to a dose of 0.2 Gm. in the tenth week of dosage.

That 0.1 Gm. per day was not sufficient to maintain the plasma quinacrine level achieved by the higher rate of intake is indicated by the lower initial level than that found before the sixteenth dose of 0.2 Gm. The plasma quinacrine concentration had dropped from its higher level and was in equilibrium with respect to the dosage rate of 0.1 Gm. per day. Hence the test dose here used results in a net gain in level over a twenty-four hour period.

All the absorption curves except the first show two peaks: an initial one at two hours and a second at six to eight hours. The flattening of the first curve after six hours suggests that even in this curve the phenomena which lead to an eight hour peak may be operative but are less prominent than later. Though scanty, the data suggest that the

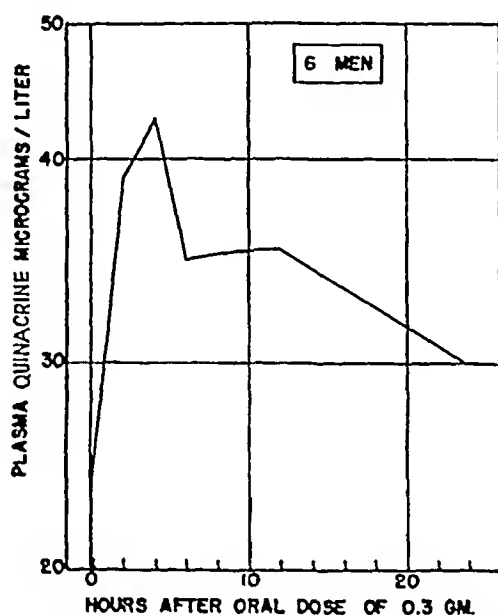


Chart 2.—Postabsorption curve of plasma quinacrine concentration following fourth daily dose of 0.3 Gm.

bimodality of the curves is real and that the second peak shows progressive intensification with continued intake of quinacrine.

The rise in the plasma quinacrine level during the first two hours after ingestion of 0.2 Gm. of the drug appears to increase from about 8 micrograms per liter after the first dose to about 13 micrograms per liter after the sixteenth dose. If this initial rise represents the flooding of the organism with quinacrine during the rapid phases of absorption and distribution, it would be expected that as the tissues become more and more saturated introduction of a given quantity would result in higher peak values.

Chart 2 presents the plasma quinacrine levels after the fourth dose of 0.3 Gm. This curve, except for the anticipated greater rise, is very similar to the curves in chart 1 where the dose was 0.2 Gm. A more

detailed discussion of the form of these curves and their mathematical expression is presented in another report.⁶

In summary, the present data indicate that after a dose of quinacrine the plasma quinacrine level rises rapidly. The major portion of the rise occurs in two hours, and the peak level is reached within eight hours. The form of the absorption curve changes with a continued intake of the drug, the delayed peak being more prominent in the late than in the early course of the dosage regimen. The increase in peak concentration over the starting level increases with continued dosage. After eight hours the plasma quinacrine level starts to fall; the rate of disappearance is more rapid at the higher levels. The net gain in level over a twenty-four hour period decreases with continued intake of the same dose, until finally the rate of disappearance comes abreast of the rate of rise and no increase in level is present at twenty-four hours.

II. PLASMA CONCENTRATIONS RESULTING FROM SEVERAL DOSAGE REGIMENS

Three types of dosage regimens were employed: (1) Uniform rate of intake of quinacrine at a suppressive dosage. Two levels of intake were studied, 0.4 Gm. per week and 0.6 Gm. per week. Approximately 100 men received each level of dosage (ARTC groups). (2) Preparatory administration at a high intake—"booster" or "priming" doses—followed by reduction to a maintenance dosage of 0.6 Gm. per week. Three priming schedules were studied: (a) The first consisted of six daily doses of 0.2 Gm. preceding the maintenance dose of 0.1 Gm. per day, six days a week (0.6 Gm. per week). This was carried out on 30 men (jungle groups A and B). (b) The second consisted of seventeen doses of 0.2 Gm. per day (8 men) (groups C1 and C2). (c) The third consisted of six doses of 0.3 Gm. per day, then six doses of 0.2 Gm. per day and finally the maintenance dose of 0.1 Gm. per day, 0.6 Gm. per week (6 men) (group C3). (3) Therapeutic levels of intake: Approximately 80 men received quinacrine according to a modification of the recommended army therapeutic schedule⁵ (ARTC group, Company B, Section 1 and Section 2).

1. *Uniform Dosage*.—Procedure: Companies B and C of the ARTC each supplied 100 men for this portion of the study. Each group of 100 men was subdivided into two sections of 50 men each. One section from each group received 0.4 Gm. of quinacrine hydrochloride per week, and the second section of each group, 0.6 Gm. per week. The dosage and bleeding schedules are given in tables 1 and 2.

Quinacrine was administered by roster at the noon mess by a medical officer assigned to the project. When Company B was placed on full

6. Brackett, F. S.: To be published.

therapeutic doses, the drug was administered at each meal. In the fourth week it was discovered that 1 subject had been able to spit out the tablet in spite of the careful supervision of administration by the officer. Thereafter, at intervals, the oral cavities were examined after administration of the drug. As an added check 6 of the men having the lowest plasma levels were given the drug in solution for a period of two weeks. During this time no change occurred in the plasma levels of these men.

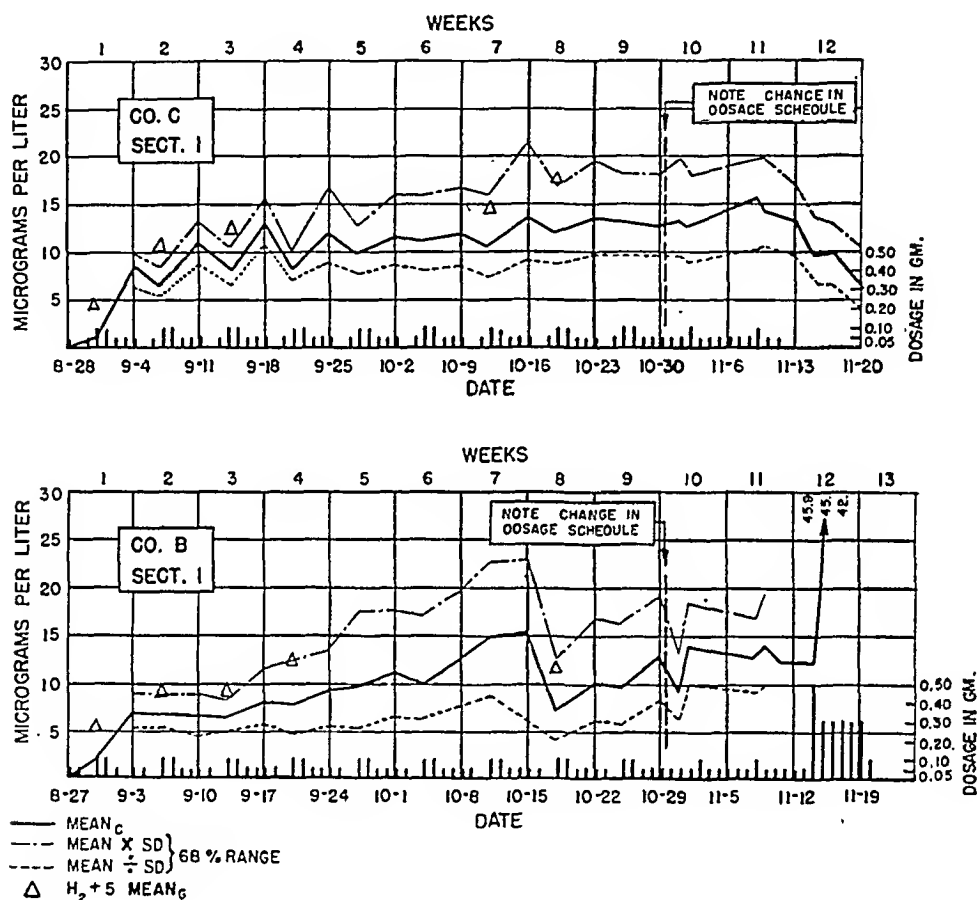


Chart 3.—MEAN_c plasma quinacrine levels of two groups of men receiving 0.4 Gm. per week.

Blood samples for underlying levels were taken at 11:30 a.m., prior to the noon mess; the first such sample of the week was designated H₁, the second H₂. The blood samples for peak concentrations were taken at 4:30 p.m., five hours after ingestion of the drug. These were designated H₂₊₅.

Results.—The characteristic behavior of the group mean plasma quinacrine levels is indicated by charts 3 and 4, which show that the time required to reach the equilibrium level was in general the same—

without regard to the magnitude of the dose.⁷ Individual variability with respect to this trend was wide, as will be seen later. For example, in two weeks approximately 8 per cent reached a level from which they did not subsequently depart significantly. Fourteen per cent appeared to have reached equilibrium levels at the end of the fourth week, whereas 9 per cent may be considered to have not yet become stabilized in seven weeks, since their highest plasma levels occurred during the eighth to eleventh weeks. When, therefore, one speaks of the attainment of equilibrium levels with a given dosage, it is to be

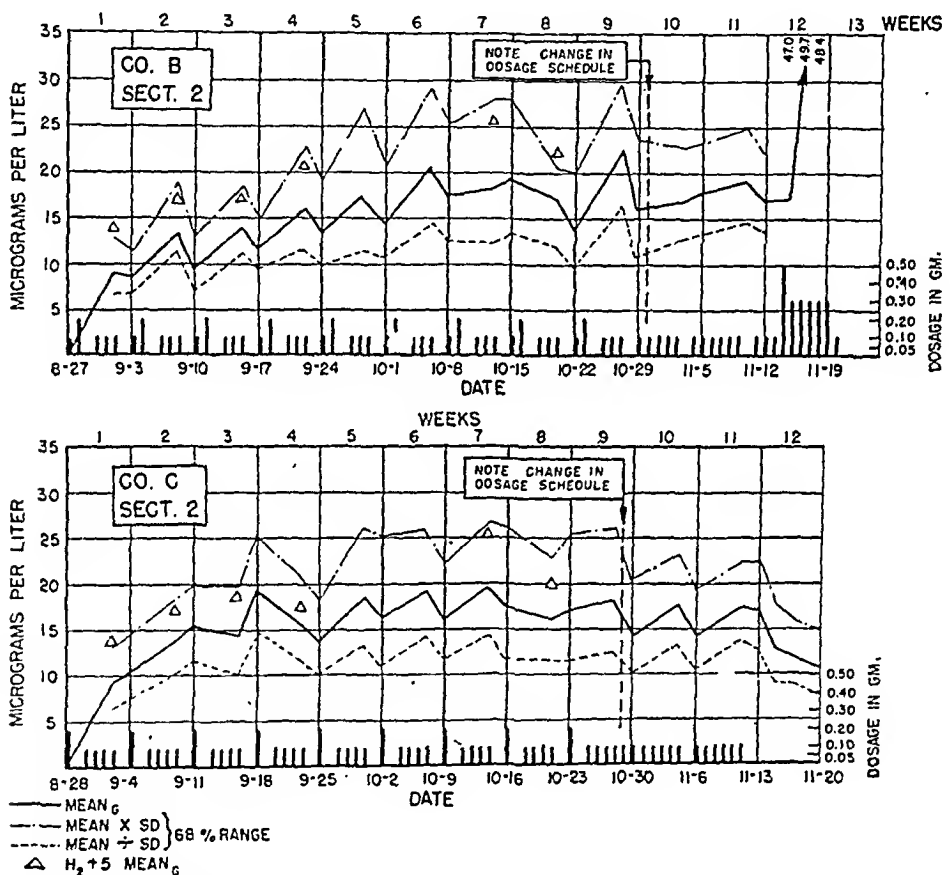


Chart 4.—MEAN_G plasma quinacrine levels of two groups of men receiving 0.6 Gm. per week.

recognized that this is a term of convenience. It remains a concept which is applicable to the mean plasma quinacrine level for a group and not to the level for an individual within the group. During the second and third weeks the rates of increase in plasma quinacrine were

7. The apparently irregular rhythmic behavior of certain groups is the result of a differing interval between dosage and sampling. The erratic results obtained on one day's sample in the week of October 15 (chart 3) and the week of October 22 (chart 4) were the result of aberrations in the chemical method which affected all samples on that day.

quite constant; accordingly, individual subjects who became stabilized in the earlier weeks in general did so at levels which were lower than those of subjects who reached their equilibrium levels in the sixth or seventh weeks.

The group mean plasma levels at equilibrium were found to be directly proportional to the dosages (chart 5); with a regimen of 0.4 Gm. per week the level was 12.2 micrograms per liter, and with 0.6 Gm. per week the mean was 17.2 micrograms per liter. These are the MEAN_G values of all H₁ measurements of weeks 7 to 11 inclusive. Alterations in time relationship between dosage and sampling may change group values. However, when the dosage pattern was changed from that regularly followed to that recommended by the Surgeon General's Office, no differences in mean plasma levels were noted (charts 3, 4

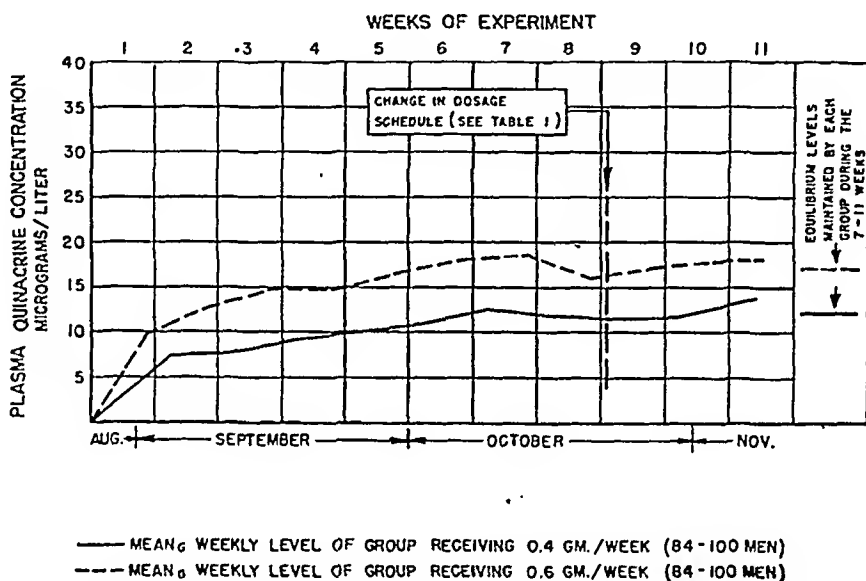


Chart 5.—Comparison of MEAN_G weekly plasma quinacrine levels of two groups of men on different dosage schedules (H₁ values).

and 6). The group data are tabulated in tables 3, 4, 5 and 6 by sections and are grouped according to dose in table 7.

2. *Effect of Initial Priming Dose.* Procedure: The experimental data illustrating the influence of priming doses are drawn from the jungle groups A and B, groups C1, C2 and C3 and the ARTC groups from Company B and Company C. After the initial priming or equivalent period the dosage of each of these groups was stabilized at a maintenance dose of 0.6 Gm. per week. The priming schedules were (in order) six daily doses of 0.2 Gm. (jungle groups A and B), seventeen daily doses of 0.2 Gm. (groups C1 and C2), six daily doses of 0.3 Gm. followed by six daily doses of 0.2 Gm. (group C3) and no priming dose (ARTC Companies B and C) (table 1).

TABLE 3.—*Mean_G and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Company B, Section 1 (Receiving 0.4 Gm. per Week)*

Week		Number of Men	Mean _G	Bleeding H ₁ 68% Range of Mean _G	Dispersion		
No.	Date				σ_G	68% Range	Mean _A
2	Sept. 3	49	6.7	6.4 - 6.9	1.32	5.1 - 8.6	6.7
3	10	48	6.3	4.8 - 6.6	1.39	4.5 - 8.8	6.4
4	17	45	8.0	7.6 - 8.4	1.39	5.8 - 11.2	8.4
5	24	43	9.1	8.4 - 9.9	1.72	5.3 - 13.2	11.4
6	Oct. 1	41	11.0	9.9 - 11.6	1.65	6.5 - 17.7	12.8
7	8	41	12.5	11.6 - 13.4	1.58	7.9 - 19.7	15.0
8	15	40	15.2	14.6 - 16.2	1.50	10.1 - 22.7	16.7
9	22	41	10.0	9.4 - 11.0	1.64	6.2 - 16.7	11.5
10	29	36	12.7	11.9 - 13.6	1.50	8.5 - 19.0	13.8
10	Nov. 2	42	13.6	12.9 - 14.2	1.36	10.0 - 18.4	14.3
11	9	41	13.8	13.1 - 14.6	1.40	9.9 - 19.4	14.7
Bleeding H ₂							
1	Aug. 30	50	1.6	1.6
2	Sept. 6	46	6.7	6.5 - 7.0	1.28	5.3 - 8.6	6.8
3	13	47	6.3	6.1 - 6.6	1.31	5.0 - 8.3	6.5
4	20	47	7.8	7.3 - 8.3	1.59	4.9 - 12.4	9.2
5	27	44	9.5	8.7 - 10.4	1.78	5.3 - 17.1	11.9
6	Oct. 4	42	10.0	9.6 - 11.1	1.65	6.3 - 17.0	11.8
7	11	41	14.7	13.8 - 15.7	1.53	8.8 - 22.5	16.3
8	18	40	7.2	6.6 - 7.9	1.73	4.2 - 12.5	9.2
9	25	42	9.6	8.9 - 13.1	1.68	5.7 - 16.2	11.2
10	Nov. 1	41	9.1	8.6 - 9.6	1.45	6.3 - 13.1	9.8
11	8	42	12.4	11.9 - 13.0	1.34	9.2 - 16.7	13.0
Bleeding H ₂ + 5							
1	Aug. 30	50	5.2	5.0 - 5.4	1.32	4.0 - 6.8	5.5
2	Sept. 6	49	7.6	7.4 - 7.9	1.29	5.9 - 9.8	7.7
3	13	44	9.0	8.5 - 9.7	1.57	5.8 - 14.2	9.1
4	20	44	12.4	11.7 - 13.1	1.49	8.3 - 18.4	13.6
5	Oct. 18	38	11.8	10.9 - 12.8	1.63	7.3 - 19.3	13.5

TABLE 4.—*Mean_G and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Company C, Section 1 (Receiving 0.4 Gm. per Week)*

Week		Number of Men	Mean _G	Bleeding H ₁ 68% Range of Mean _G	Dispersion		
No.	Date				σ_G	68% Range	Mean _A
2	Sept. 4	45	8.5	8.4 - 8.7	1.16	7.4 - 9.9	8.6
3	11	48	10.7	10.4 - 10.9	1.24	8.6 - 13.3	10.9
4	18	44	13.1	12.8 - 13.2	1.20	10.9 - 16.5	13.3
5	25	41	12.1	11.7 - 12.7	1.36	8.9 - 16.5	12.7
6	Oct. 2	43	11.6	11.0 - 12.1	1.36	8.6 - 15.8	12.3
7	9	40	12.0	11.4 - 12.7	1.41	8.5 - 16.9	12.9
8	16	43	13.9	13.0 - 14.9	1.56	9.0 - 21.6	15.4
9	23	42	13.5	12.8 - 14.2	1.41	9.6 - 19.0	14.4
10	30	39	12.7	12.0 - 13.4	1.41	9.0 - 17.8	13.6
10	Nov. 3	42	12.7	12.1 - 13.4	1.42	8.9 - 18.0	13.6
11	10	42	14.3	13.6 - 15.0	1.36	10.5 - 19.4	15.0
Bleeding H ₂							
1	Aug. 31	42	1.0
2	Sept. 7	45	6.7	6.5 - 6.8	1.26	5.3 - 8.4	6.9
3	14	47	8.3	8.0 - 8.6	1.27	6.5 - 10.5	8.5
4	21	41	8.5	8.3 - 8.7	1.19	7.2 - 10.1	8.7
5	28	43	9.8	9.4 - 10.1	1.29	7.6 - 12.6	10.5
6	Oct. 5	42	11.2	10.7 - 11.8	1.41	8.0 - 15.8	12.1
7	12	40	10.6	10.0 - 11.4	1.50	7.1 - 16.0	11.8
8	19	42	12.0	11.4 - 12.7	1.40	8.6 - 16.8	14.3
9	26	39	13.1	12.5 - 13.8	1.38	9.5 - 18.1	13.8
10	Nov. 2	42	13.2	12.8 - 14.1	1.46	9.0 - 19.3	14.2
11	9	40	13.8	13.1 - 14.5	1.38	10.0 - 19.0	14.6
Bleeding H ₂ + 5							
1	Aug. 31	47	4.6	4.4 - 4.8	1.39	3.3 - 6.4	4.9
2	Sept. 7	46	10.7	10.4 - 11.1	1.23	8.7 - 13.2	10.9
3	14	46	12.3	11.9 - 12.7	1.24	9.9 - 15.2	12.6
4	21	41	11.1	10.7 - 11.5	1.24	8.9 - 13.8	11.4
5	Oct. 12	37	14.4	13.5 - 15.2	1.48	9.7 - 21.3	16.5
6	19	41	17.9	17.1 - 18.8	1.34	13.4 - 24.0	18.7

TABLE 5.—*Mean_G and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Company B, Section 2 (Receiving 0.6 Gm. per Week)*

Week		Number of Men	Bleeding H ₁		Dispersion		
No.	Date		Mean _G	68% Range of Mean _G	σ _G	68% Range	Mean _A
2	Sept. 3	47	8.9	8.6 - 9.3	1.28	6.9 - 11.4	8.8
3	10	45	9.6	9.2 - 10.0	1.43	7.1 - 12.9	9.8
4	17	42	11.8	11.4 - 12.2	1.25	9.5 - 14.7	11.6
5	24	41	13.6	12.9 - 14.3	1.37	9.9 - 18.6	15.1
6	Oct. 1	45	14.7	14.0 - 15.5	1.39	10.6 - 20.5	15.9
7	8	41	17.5	16.5 - 18.4	1.41	12.3 - 24.7	18.7
8	15	40	19.3	18.2 - 20.6	1.46	13.2 - 28.3	18.8
9	22	40	13.6	12.8 - 14.4	1.46	9.3 - 19.8	14.7
10	29	42	16.0	15.0 - 17.0	1.48	10.8 - 23.7	17.0
11	Nov. 5	41	17.9	17.2 - 18.7	1.31	13.7 - 23.6	19.9
12	12	40	17.5	16.9 - 18.2	1.28	13.7 - 22.3	18.1
Bleeding H ₂							
1	Sept. 1	49	9.2	8.8 - 9.7	1.37	6.7 - 12.7	10.0
2	8	45	13.9	13.3 - 14.3	1.25	11.1 - 17.2	13.4
3	15	43	14.2	13.6 - 14.8	1.30	10.9 - 18.4	14.0
4	22	43	16.2	15.4 - 17.1	1.41	11.5 - 22.8	16.0
5	29	44	17.5	16.4 - 18.8	1.56	11.2 - 26.8	18.8
6	Oct. 6	43	20.4	19.3 - 23.1	1.42	14.3 - 29.0	21.8
7	13	44	18.3	17.2 - 19.5	1.58	12.1 - 27.7	21.5
8	20	42	17.3	16.3 - 18.4	1.48	11.7 - 20.3	16.7
9	27	43	22.4	21.4 - 23.3	1.32	16.1 - 29.5	23.5
10	Nov. 3	41	16.9	16.2 - 16.7	1.35	12.6 - 22.8	17.7
11	10	41	19.0	18.1 - 19.7	1.30	14.5 - 24.6	19.6
Bleeding H ₂ + 5							
1	Sept. 1	48	14.1	13.6 - 14.7	1.33	8.5 - 18.8	14.0
2	8	45	16.9	16.3 - 17.6	1.32	12.8 - 22.5	17.0
3	15	44	17.3	16.6 - 18.0	1.29	13.3 - 22.4	18.1
4	22	43	20.8	20.1 - 21.8	1.33	15.7 - 27.7	20.5
7	Oct. 13	44	25.9	24.6 - 27.2	1.39	18.7 - 35.7	28.1
8	20	41	22.1	21.0 - 23.2	1.37	16.1 - 30.3	21.4

TABLE 6.—*Mean_G and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Company C, Section 2 (Receiving 0.6 Gm. per Week)*

Week		Number of Men	Bleeding H ₁		Dispersion		
No.	Date		Mean _G	68% Range of Mean _G	σ _G	68% Range	Mean _A
2	Sept. 4	52	11.2	10.9 - 11.5	1.35	9.0 - 13.9	12.0
3	11	51	15.1	14.5 - 15.6	1.35	11.5 - 19.7	15.6
4	18	48	19.1	18.4 - 20.0	1.31	14.6 - 25.0	19.8
5	25	45	13.6	13.0 - 14.2	1.35	10.0 - 18.3	14.3
6	Oct. 2	46	16.3	15.3 - 16.8	1.54	10.6 - 25.1	17.6
7	9	46	16.9	15.3 - 16.8	1.37	11.7 - 21.9	16.8
8	16	42	17.5	16.4 - 18.6	1.49	11.7 - 26.1	18.8
9	23	44	17.0	16.0 - 18.0	1.49	11.4 - 25.3	18.5
10	30	44	14.4	13.6 - 15.2	1.42	10.1 - 20.5	15.3
11	Nov. 6	44	14.3	13.6 - 14.9	1.35	10.6 - 19.2	15.0
12	13	44	17.0	16.3 - 17.8	1.35	12.8 - 22.5	17.6
Bleeding H ₂							
1	Sept. 2	53	9.1	8.7 - 9.6	1.44	6.4 - 13.1	9.6
2	9	50	13.7	13.1 - 14.3	1.34	10.2 - 18.4	14.2
3	16	45	14.4	13.8 - 15.1	1.38	10.0 - 19.8	15.2
4	23	47	15.4	14.7 - 16.1	1.24	11.5 - 20.6	16.2
5	30	46	18.6	18.5 - 19.7	1.40	13.3 - 26.0	19.9
6	Oct. 7	46	19.3	18.7 - 20.5	1.34	14.4 - 25.9	20.2
7	14	47	19.6	18.7 - 20.5	1.36	14.4 - 26.7	23.0
8	21	44	16.0	15.2 - 16.9	1.42	11.3 - 22.7	17.0
9	28	45	17.8	16.9 - 18.9	1.46	12.3 - 26.0	19.1
10	Nov. 4	44	17.6	16.9 - 18.4	1.32	13.4 - 23.3	18.5
11	11	45	17.4	16.8 - 18.1	1.28	13.7 - 22.2	17.9
Bleeding H ₂ + 5							
1	Sept. 2	52	13.8	13.2 - 14.4	1.37	10.0 - 18.9	12.0
2	9	51	17.2	16.5 - 18.0	1.35	12.8 - 23.3	16.1
3	16	46	18.6	17.8 - 19.5	1.36	13.7 - 25.3	19.6
4	23	47	17.5	16.6 - 18.3	1.42	12.3 - 24.9	18.6
7	Oct. 14	45	25.5	24.4 - 26.7	1.36	18.8 - 34.8	26.8
8	21	44	20.0	19.0 - 21.0	1.36	14.4 - 27.7	21.1

Results.—The plasma quinacrine concentrations resulting from intakes according to these schedules are shown in chart 6. In all cases in which a priming regimen (curves 2, 3 and 4) was used a higher plasma concentration was present at the end of the first week than when no

TABLE 7.—*Mean_G and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter); Tabulated Data for Combined ARTC Groups—Sections 1 and 2 of Companies B and C*

Groups Receiving 0.40 Gm. per Week							
		Bleeding H ₁			Dispersion		
No.	Week Date	Number of Men	Mean _G	68% Range of Mean _G	σ _G	68% Range	Mean _A
2	Sept. 3 & 4	94	7.5	7.3 - 7.7	1.29	5.8 - 9.7	7.8
3	10 & 11	96	8.2	7.9 - 8.5	1.47	5.6 - 12.0	8.8
4	17 & 18	89	10.2	9.9 - 10.6	1.43	7.1 - 14.7	10.9
5	24 & 25	84	10.4	9.9 - 11.0	1.59	6.6 - 16.7	12.1
6	Oct. 1 & 2	84	11.0	10.6 - 11.5	1.52	7.3 - 16.7	12.5
7	8 & 9	81	12.5	11.7 - 13.1	1.50	8.3 - 18.8	13.9
8	15 & 16	83	14.5	13.8 - 15.2	1.53	9.5 - 22.2	15.5
9	22 & 23	83	11.7	11.2 - 12.3	1.56	7.5 - 18.4	13.0
10	29 & 30	75	12.7	12.2 - 13.2	1.45	8.7 - 18.4	13.7
10	Nov. 2 & 3	84	13.1	12.6 - 13.6	1.40	9.4 - 18.3	13.9
11	9 & 10	83	14.0	13.5 - 14.5	1.38	10.2 - 19.3	14.7
Bleeding H ₂							
2	Sept. 6 & 7	91	6.7	6.6 - 6.9	1.27	5.3 - 8.5	6.9
3	13 & 14	94	7.2	7.1 - 7.4	1.29	5.6 - 9.3	7.5
4	20 & 21	88	8.1	7.8 - 8.4	1.43	5.7 - 11.7	9.0
5	27 & 28	87	9.6	9.2 - 10.1	1.53	6.1 - 15.2	11.2
6	Oct. 4 & 5	84	10.8	10.2 - 11.3	1.54	7.0 - 16.5	11.9
7	11 & 12	81	12.5	11.8 - 13.3	1.56	8.0 - 19.6	14.1
8	18 & 19	82	9.4	9.0 - 9.8	1.53	6.1 - 14.4	11.8
9	25 & 26	81	11.2	10.6 - 11.8	1.58	7.1 - 17.7	12.4
10	Nov. 1 & 2	83	11.0	10.5 - 11.5	1.52	7.2 - 16.7	11.7
11	8 & 9	82	13.0	12.6 - 13.5	1.37	9.5 - 17.8	13.8
Groups Receiving 0.60 Gm. per Week							
Bleeding H ₁							
2	Sept. 3 & 4	99	10.0	9.7 - 10.4	1.30	7.7 - 13.1	10.6
3	10 & 11	96	12.2	11.8 - 12.6	1.34	9.1 - 16.3	12.8
4	17 & 18	90	15.3	14.9 - 15.7	1.30	11.8 - 19.8	15.9
5	24 & 25	86	13.6	13.2 - 14.0	1.33	10.2 - 18.0	14.7
6	Oct. 1 & 2	91	15.5	14.9 - 16.1	1.48	10.5 - 22.8	16.7
7	8 & 9	87	16.7	16.1 - 17.3	1.43	11.7 - 23.9	17.7
8	15 & 16	82	18.4	17.6 - 19.2	1.48	12.4 - 27.3	20.0
9	22 & 23	84	15.3	14.6 - 16.0	1.50	10.2 - 22.9	16.6
10	29 & 30	86	15.1	14.5 - 15.8	1.46	10.3 - 22.1	15.6
11	Nov. 5 & 6	84	16.5	15.9 - 17.0	1.35	12.2 - 22.2	17.5
Bleeding H ₂							
1	Sept. 1 & 2	102	9.1	8.8 - 9.4	1.41	6.5 - 12.8	9.8
2	8 & 9	95	13.7	13.2 - 14.3	1.30	10.6 - 17.8	14.1
3	15 & 16	83	14.3	13.9 - 14.8	1.34	10.7 - 19.2	14.9
4	22 & 23	90	15.8	15.3 - 16.3	1.37	11.5 - 21.6	16.7
5	29 & 30	90	18.1	17.3 - 18.8	1.49	12.5 - 26.8	19.3
6	Oct. 6 & 7	89	19.8	19.1 - 20.5	1.39	14.3 - 27.4	21.0
7	13 & 14	91	18.9	18.2 - 19.7	1.44	13.1 - 27.3	22.2
8	20 & 21	86	16.6	16.0 - 17.3	1.45	11.4 - 24.1	17.9
9	27 & 28	83	19.9	19.2 - 20.7	1.42	14.0 - 28.3	19.3
10	Nov. 3 & 4	85	17.3	16.8 - 17.8	1.33	13.0 - 23.0	18.1
11	10 & 11	86	18.1	17.6 - 18.6	1.29	14.0 - 23.4	18.7

priming dose was given (curve 1). Compare the curve (curve 1) of the mean plasma level for the ARTC group on a constant schedule of 0.6 Gm. per week with the curve (curve 2) for the jungle group, which received an initial booster dose of 1.2 Gm. per week for the first week. In the groups C1 and C2 (curve 3) and group C3 (curve 4) plasma concentrations in excess of the ultimate maintenance level were reached

within a week. However, the time required to reach the final equilibrium plasma quinacrine level was not changed. Instead it was approached by a declining concentration curve from higher levels in contrast to the progressively rising curves for the group receiving no booster dose. The jungle group (curve 2), receiving twice the maintenance dose for the first week, reached a plasma concentration close to its final equilibrium level at the end of the first week, declined slightly during the second week and thereafter was in close agreement with the level of the ARTC group (curve 1) receiving maintenance dosage from the outset. The equilibrium levels finally attained on the maintenance regimen of

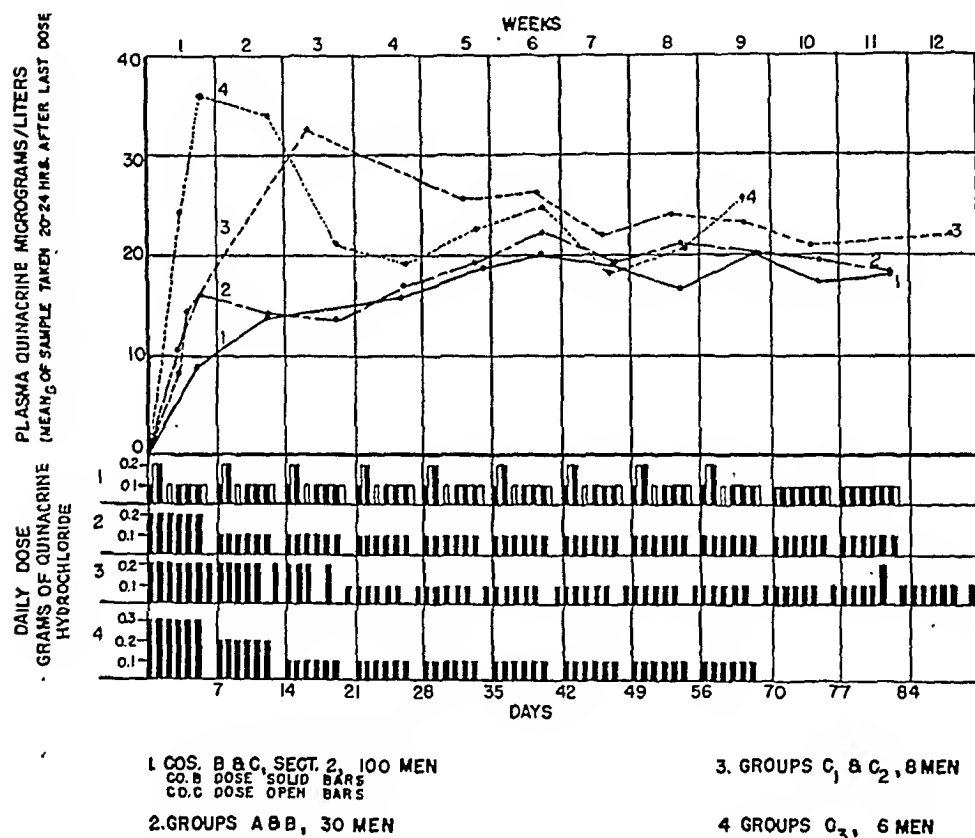


Chart 6.—Plasma quinacrine levels obtained with different priming doses (maintenance dosage, 0.6 Gm. per week).

0.6 Gm. per week did not differ significantly among the four groups. Since the rapidity with which an effective suppressive plasma quinacrine level is reached may be an important factor in operations in malarious areas, the practical significance of initial high dosage schedules is great.

Of considerable practical advantage in the design of such schedules is the technic of prediction of plasma concentration as a function of dosage as given in section IV. For example, the rate of rise in plasma level in any week is approximately 50 per cent of the difference between the level already established and the final equilibrium level. Then

for dosages of 0.6 Gm. per week and 1.2 Gm. per week the predicted plasma levels at the end of succeeding weeks will be:

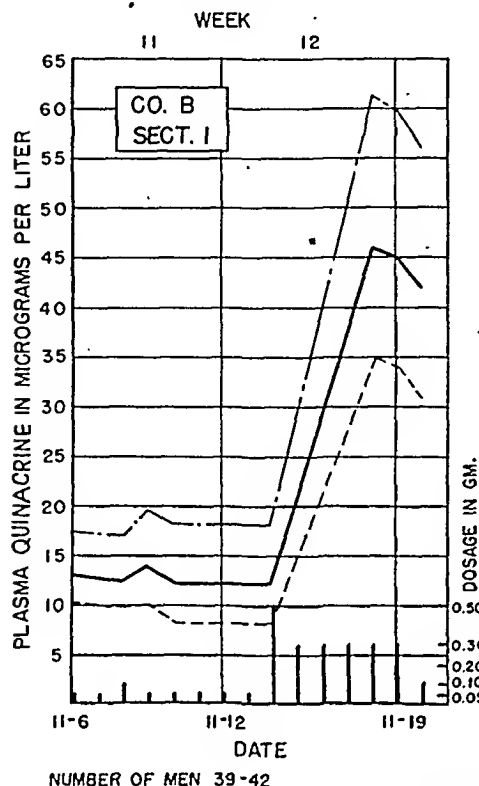
Week	Plasma Concentration	
	0.6 Gm./Wk.	1.2 Gm./Wk.
1.....	9.0	18.0
2.....	13.5	27.0
3.....	15.7	31.5
4.....	16.9	33.7
5.....	17.4	34.8
Equilibrium.....	18.0	36.0

At the higher dosage rate of 1.2 Gm. per week the plasma level at the end of the first week is as high as the equilibrium level ultimately attained by a dosage of 0.6 Gm. per week. Thus, if the dosage during the first week is twice the subsequent maintenance dosage, the plasma concentration will be raised to the desired level in one week rather than in the five to seven weeks which are required when no "booster" dose is given.

3. *Plasma Levels Obtained with Therapeutic Doses.*—Procedure: After having reached equilibrium levels on their respective dosage schedules of 0.4 Gm. per week and 0.6 Gm. per week, the two sections of Company B, ARTC group, were placed on a modified therapeutic regimen at the beginning of the twelfth week. The dosage schedule was as follows: the first day, 0.5 Gm. (0.1 Gm. at breakfast and 0.2 Gm. at lunch and supper); the next five days, 0.3 Gm. (0.1 Gm. at breakfast, lunch and supper), and the seventh day, 0.1 Gm. at breakfast. Blood samples were taken before the noon meal on the fourth, fifth and sixth days.

Results.—The increases in plasma levels for the two sections at the end of six days were approximately the same, 30.8 and 30.5 micrograms per liter respectively above their previously established equilibrium levels (chart 7). The changes in plasma concentration induced by the therapeutic dosage regimen followed the same basic law of build-up as that previously determined for suppressive regimens with lower doses. An important objective was to determine whether men with persisting low or high plasma levels while on suppressive therapy would continue in the same relation to the group mean when receiving therapeutic doses of quinacrine. The correlations are shown in charts 8 and 9. Chart 8 shows the distribution of the equilibrium levels attained under the two suppressive regimens and the subsequent distribution of the low, central and high levels following the institution of therapeutic doses. No great shift in distribution occurred; the plasma levels tended to retain their original relationship to each other. The correlation is shown in another way in chart 9, where the level attained by therapeutic doses is plotted against the level attained on suppressive doses. A definite relationship is evident, but the correlation is not high. One

THERAPEUTIC DOSAGE AFTER RECEIVING
0.4 GRAMS PER WEEK FOR ELEVEN WEEKS



THERAPEUTIC DOSAGE AFTER RECEIVING
0.6 GRAMS PER WEEK FOR ELEVEN WEEKS

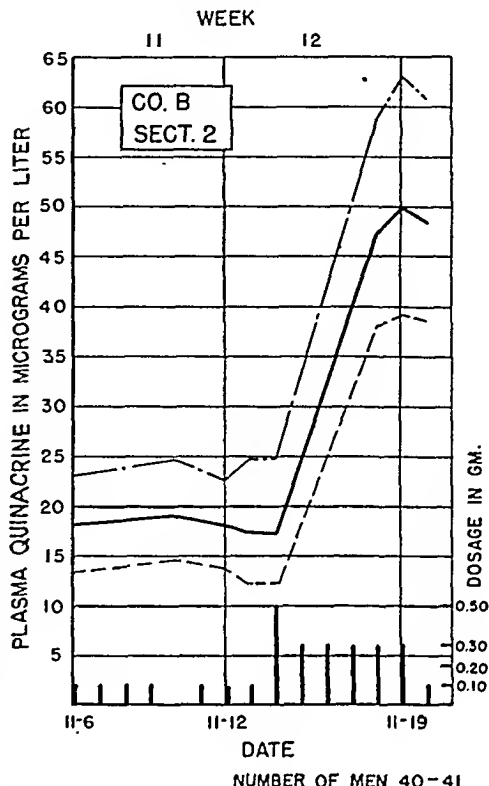


Chart 7.—MEAN_G plasma quinacrine levels of two groups of men receiving therapeutic dosage for one week.

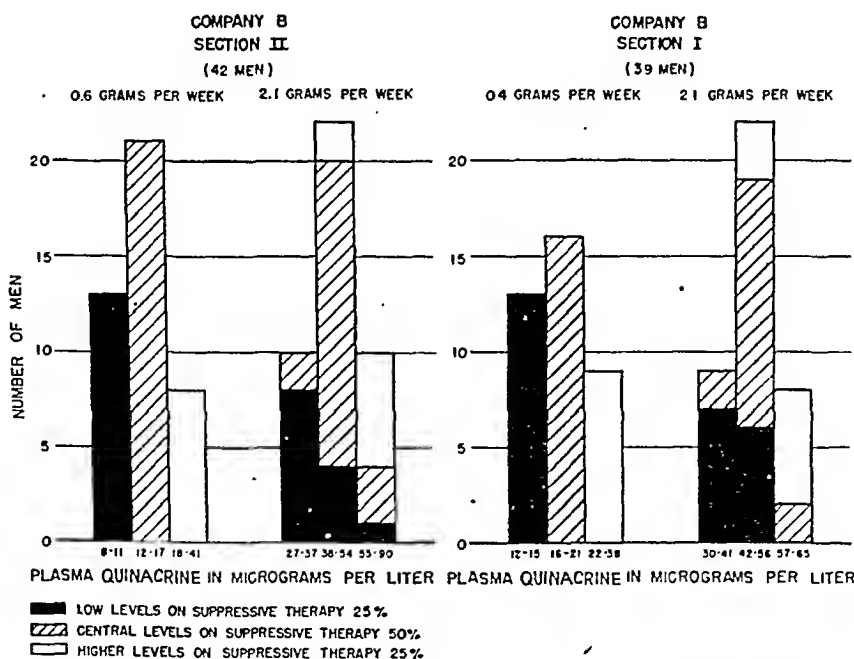
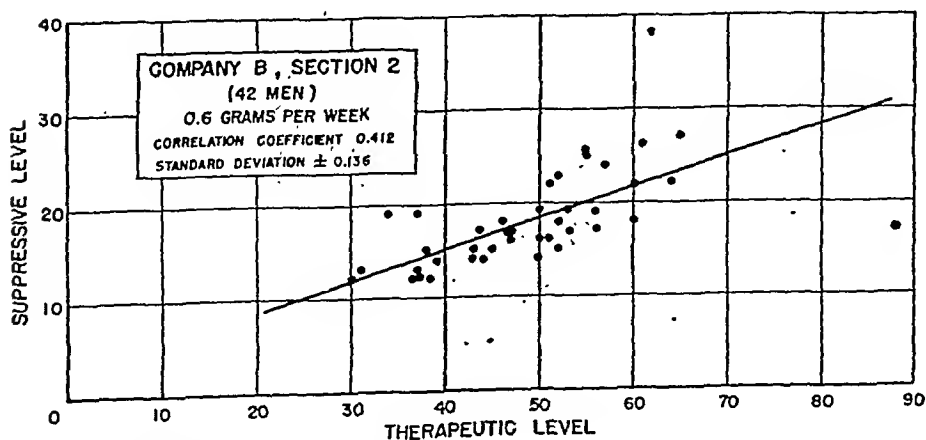
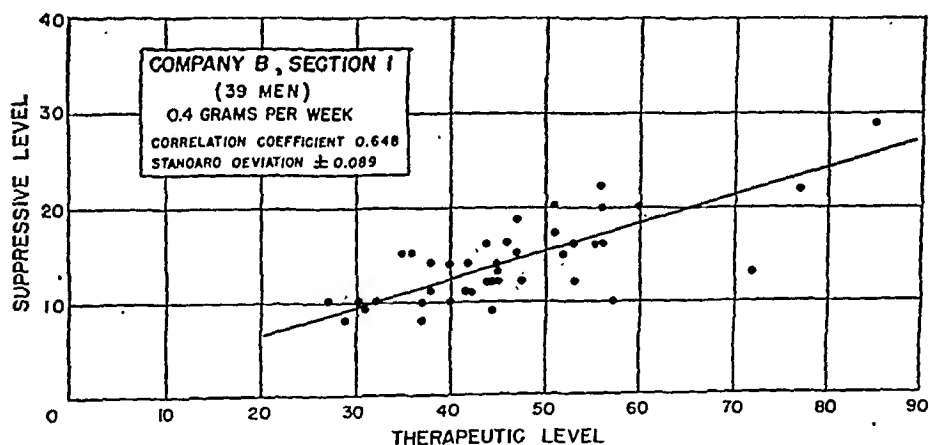


Chart 8.—Relationship between the level attained on suppressive therapy and the level reached on therapeutic doses.

cannot predict with certainty the relative level for a subject receiving therapeutic doses from his relative level while on suppressive doses, except in broad categories. The group data are assembled in table 8.

TABLE 8.—*Plasma Quinacrine Levels (Micrograms per Liter) of Group of Men (Company B) Receiving Therapeutic Dosage After Eleven Weeks of Suppressive Dosage*

Company B Section 1							
Week		Number of Men	Mean _G	68% Range of Mean _G	Dispersion		
No.	Date				σ_G	68% Range	Mean _A
12	Nov. 18	42	45.9	44.0 - 48.0	1.33	34.6 - 61.0	47.9
13	19	41	45.0	43.1 - 47.1	1.33	33.8 - 59.8	47.0
13	20	39	42.0	40.1 - 44.0	1.33	30.8 - 56.0	46.6
Company B Section 2							
12	Nov. 18	40	47.0	43.1 - 48.6	1.25	37.7 - 58.5	48.1
13	19	41	49.7	47.8 - 51.5	1.27	39.0 - 63.2	51.1
13	20	41	48.4	46.7 - 50.1	1.26	38.6 - 60.8	49.6



BOTH GROUPS RECEIVED 2.1 GRAMS PER WEEK
ON THE THERAPEUTIC REGIMEN

Chart 9.—Relationship between the plasma quinacrine level attained on suppressive therapy and the level reached on therapeutic doses.

III. PLASMA CONCENTRATIONS AFTER CESSATION OF DOSAGE AND AFTER INTERRUPTION OF DOSAGE

Procedure.—At the end of the eleventh week jungle group B was removed from the humid heat, and administration of quinacrine to both groups was discontinued in order to study the rate of fall of the plasma quinacrine level (die-away). The subsequent increase in concentration on restoration of suppressive doses of quinacrine (build-up) at different points on the plasma die-away curve was also determined. Half of the men were without the drug for one week and the other half for two weeks. To insure comparability of the two die-away curves, groups A and B were rearranged into two new groups (X and Y) which were comparable with respect to: duration of previous exposure to heat, time since removal from the humid heat, weight of the men, plasma quinacrine level over the four week period before cessation of dosage and quinacrine levels after six days without the drug. Quinacrine in suppressive doses (0.1 Gm. per day) was resumed in group X after an interval of one week and in group Y after two weeks.

To obtain additional information on larger numbers of men concerning the die-away curve of plasma quinacrine after cessation of dosage the drug was discontinued in ARTC groups Company C, Section 1 (0.4 Gm. per week) and Company C, Section 2 (0.6 Gm. per week) for one week after eleven weeks of suppressive therapy. Blood samples were obtained at the beginning, middle and end of the week.

Results.—Die-away: After the intake of quinacrine has been discontinued, the plasma concentration of quinacrine falls off according to a normal decay curve, rapidly at first, then progressively more slowly as the level approaches zero. The pattern of disappearance indicates a rate of elimination and degradation which is proportional to the level. The slow rate of disappearance is consonant with the observed slow attainment of equilibrium levels and probably results from two characteristic features of quinacrine metabolism, the extensive tissue storage and the very low concentration in plasma. These two factors, the large amount to be disposed of and low carrying capacity in the path of elimination, combine to produce a slow rate of disappearance of the drug. Chart 10 shows the fall in plasma level in groups X and Y. Chart 11 shows the plasma decay curves for the larger ARTC groups. The latter data plotted on semilogarithmic scale in chart 12 illustrate the exponential nature of the disappearance of quinacrine from the plasma. The slopes of the lines indicate a 10 per cent reduction in plasma level per day, a 50 per cent reduction per week and a 75 per cent reduction in two weeks. This is very similar to the rate of approach to equilibrium levels for a uniform rate of intake. The theoretic basis for this is considered in another report⁶ and in section IV. The means

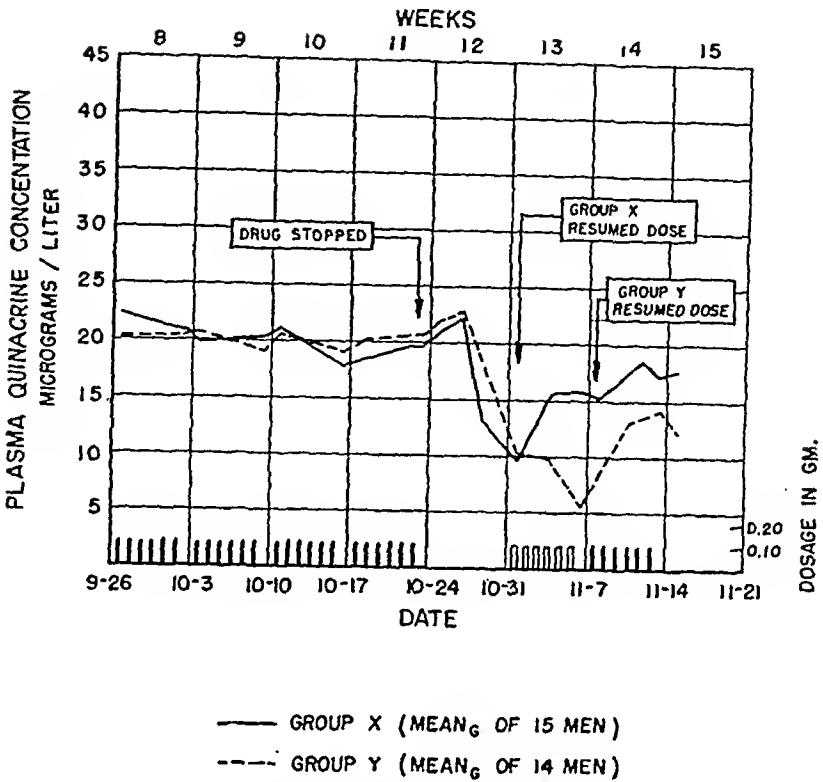


Chart 10.—Influence of the interruption of dosage on the plasma quinacrine levels (30 men receiving weekly dosage of 0.6 Gm.).

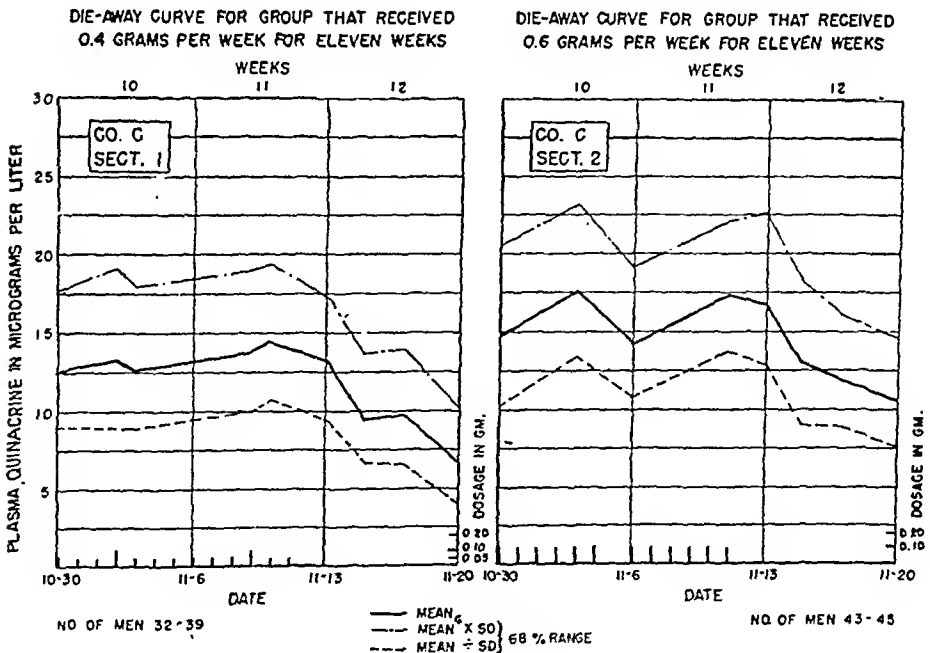
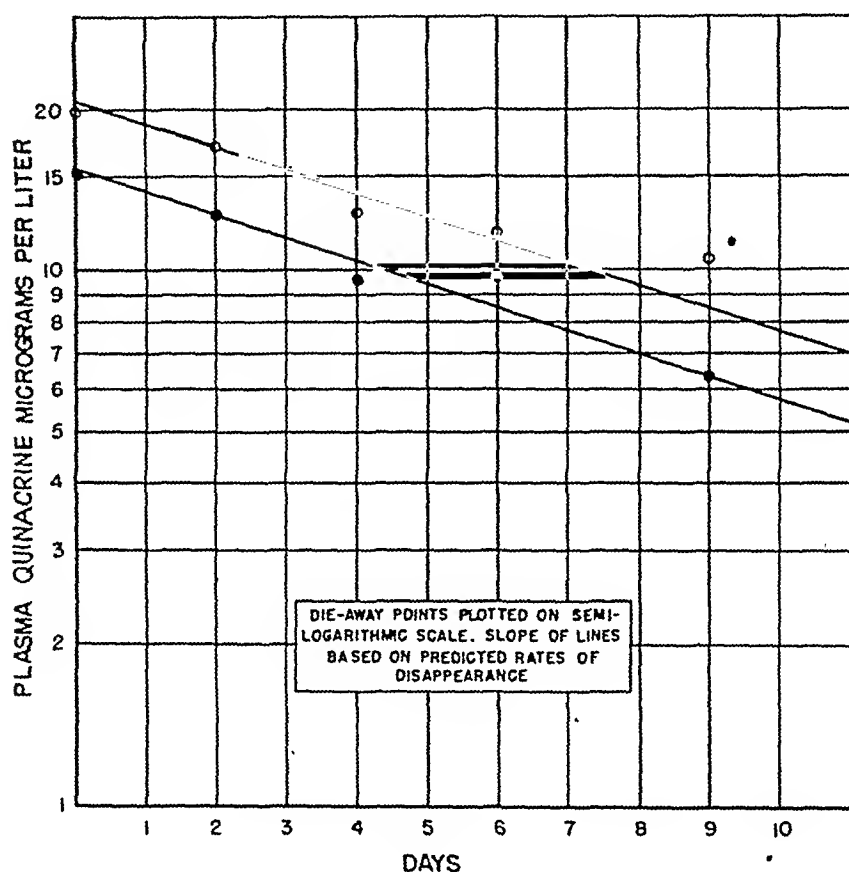


Chart 11.—MEAN_G plasma quinacrine levels of two groups of men for one week after discontinuance of suppressive therapy.

and dispersions for the X and Y groups are recorded in table 9 and the die-away data for the ARTC groups in table 10.

Interruption of Dosage.—After quinacrine had been discontinued in group X for one week and in group Y for two weeks, dosage was resumed according to the previous schedule of 0.6 Gm. per week. The results are shown in chart 10. In each instance the rate of increase in the plasma levels of quinacrine was consonant with the findings in other groups at the start of dosage taking into account the higher start-



COMPANY C, SECTION 2 ○ (0.6 GM. GROUP)

COMPANY C, SECTION 1 ● (0.4 GM. GROUP)

Chart 12.—Exponential nature of the disappearance of quinacrine from the plasma when dosage is discontinued.

ing levels; this is also illustrated by the close correspondence of the observed rate of build-up with predicted rates of build-up as shown in chart 20. It appears, therefore, that reestablishment of suppressive levels after interruption of dosage presents no unique features; if dosage is resumed while quinacrine is still present in the plasma, the return to equilibrium levels will be hastened in proportion to the plasma quinacrine level when dosage is resumed.

TABLE 9.—*Mean Plasma Quinacrine Levels of Men in the Jungle Group Rearranged for Study of Die-Away and Recovery (H₁ and H₂ Bleedings Only)*

All Bleedings Group X							
Week		Number of Men	Mean _G	68% Range of Mean _G	Dispersion		
No.	Date				σ _G	68% Range	Mean _A
8	Sept. 27	14	22.2	19.9 - 24.8	1.51	14.8 - 33.5	24.1
8	Oct. 2	15	20.7	19.0 - 22.6	1.40	14.7 - 29.0	22.0
9	4	15	19.9	18.0 - 21.9	1.46	13.7 - 29.0	21.5
9	9	14	20.3	17.3 - 22.1	1.45	16.6 - 34.8	21.8
10	11	15	21.1	19.4 - 23.0	1.39	15.2 - 29.4	22.3
10	16	14	17.7	16.1 - 19.4	1.41	12.5 - 25.0	18.8
11	18	15	14.5	13.2 - 15.8	1.42	10.2 - 20.5	15.3
11	23	15	19.7	18.4 - 21.4	1.31	15.0 - 25.9	20.5
Last dose October 23							
11	Oct. 24	15	25.5	23.8 - 27.2	1.29	19.6 - 33.0	26.3
12	25	14	21.1	19.6 - 22.7	1.34	16.1 - 27.6	21.8
12	27	14	22.2	20.7 - 23.9	1.32	16.9 - 29.3	23.0
12	29	14	13.0	11.8 - 14.4	1.45	8.9 - 18.9	13.8
13	Nov. 1	14	9.6	8.6 - 10.9	1.50	6.4 - 14.4	10.3
Dosage resumed November 1							
13	Nov. 4	14	15.5	14.3 - 16.8	1.34	11.5 - 20.8	16.1
13	6	15	15.7	14.5 - 17.1	1.38	11.4 - 21.8	16.5
14	8	15	15.3	14.4 - 16.3	1.28	11.9 - 19.7	15.8
14	11	15	18.5	17.3 - 19.7	1.28	14.4 - 23.6	19.0
14	13	15	17.3	16.3 - 18.8	1.26	13.7 - 21.9	17.8
15	15	15	17.6	16.6 - 18.8	1.27	13.9 - 22.3	18.1
All Bleedings Group Y							
8	Sept. 27	14	20.1	18.8 - 21.6	1.30	15.5 - 26.2	20.8
8	Oct. 2	14	20.4	18.5 - 22.5	1.45	14.0 - 29.6	21.5
9	4	14	20.7	19.3 - 22.0	1.28	16.2 - 26.4	21.2
9	9	14	19.1	17.9 - 20.3	1.28	14.9 - 24.3	19.6
10	11	14	20.4	19.3 - 21.6	1.23	16.6 - 25.2	20.5
10	16	13	19.2	17.5 - 21.2	1.41	13.7 - 23.1	20.3
11	18	13	14.7	13.9 - 16.0	1.38	10.7 - 20.2	15.4
11	23	14	20.8	19.5 - 22.2	1.27	16.4 - 26.4	21.3
Last dose October 23							
11	Oct. 24	14	24.3	22.9 - 25.7	1.25	19.5 - 30.2	24.8
12	25	14	22.0	20.5 - 23.0	1.24	17.7 - 27.4	22.5
12	27	13	24.8	23.1 - 26.8	1.31	19.0 - 32.5	25.7
12	29	13	13.5	12.5 - 14.5	1.30	10.4 - 17.5	13.8
13	Nov. 1	14	10.1	9.1 - 11.0	1.42	7.1 - 14.3	10.6
13	4	14	9.9	9.1 - 10.8	1.37	7.2 - 13.7	10.6
13	6	13	5.7	4.9 - 6.5	1.63	3.5 - 9.2	6.3
14	8	14	7.5	6.9 - 8.2	1.40	5.4 - 10.6	7.9
Dosage resumed November 8							
14	Nov. 11	14	13.0	12.2 - 14.0	1.30	10.1 - 16.7	13.4
14	13	14	14.0	12.9 - 14.5	1.25	11.0 - 17.1	14.0
15	15	14	12.4	11.7 - 13.2	1.26	9.8 - 15.7	12.7

TABLE 10.—*Plasma Quinacrine Levels (Micrograms per Liter) of Group of Men (Company C) Receiving No Drug After Eleven Weeks of Suppressive Dosage*

Company C Section 1							
Week		Number of Men	Mean _G	68% Range of Mean _G	Dispersion		
No.	Date				σ _G	68% Range	Mean _A
12	Nov. 13	32	12.8	12.8 - 13.4	1.34	9.5 - 17.1	13.5
12	15	39	9.6	9.0 - 10.1	1.42	6.7 - 13.6	10.2
12	17	39	9.8	8.6 - 9.6	1.42	6.4 - 12.9	9.6
13	20	39	6.3	5.8 - 6.8	1.67	3.8 - 10.5	7.2
Company C Section 2							
12	Nov. 13	44	17.0	16.3 - 17.8	1.33	12.8 - 22.5	17.6
12	15	45	12.8	12.1 - 13.5	1.41	9.1 - 18.0	13.5
12	17	43	11.8	11.3 - 12.4	1.34	8.9 - 15.8	12.3
13	20	44	10.5	10.0 - 11.0	1.39	7.6 - 14.6	11.1

IV. INDIVIDUAL VARIATION OF PLASMA CONCENTRATION AND PREDICTION OF CONCENTRATION

Individual Variation.—Subjects on the same dosage regimen may differ markedly in their plasma quinacrine concentrations. For example, in a group of 85 men on a regimen of 0.4 Gm. per week the equilibrium plasma quinacrine levels were distributed as shown in chart 13. In order to describe the distribution pattern and the variability of the plasma levels, statistical treatment of the data has been employed. It is immediately evident from the unsymmetric pattern in chart 13 that the variability in plasma levels does not follow the normal arithmetic probability distribution. Therefore the arithmetic mean and the standard deviation, which apply to the normal arithmetic probability curve,

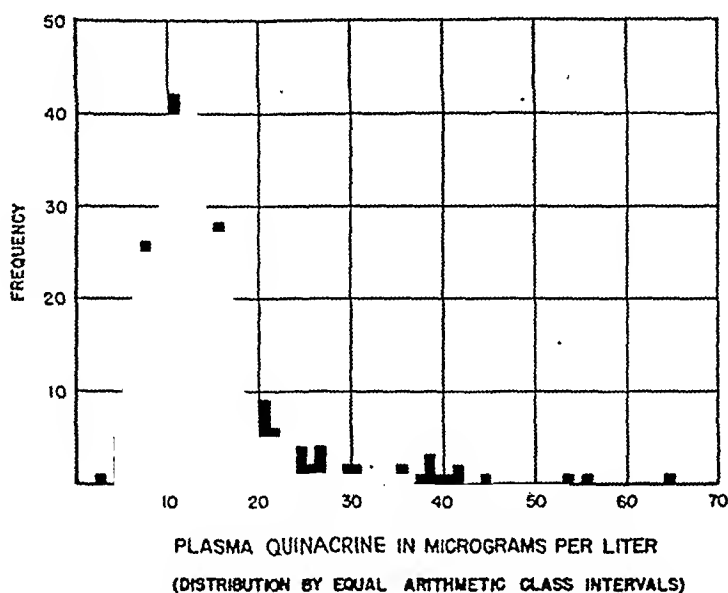


Chart 13.—Frequency distribution of plasma quinacrine levels in Company B, Section 1, seventh through eleventh week.

are not suitable to describe the distribution of the individual plasma quinacrine levels. When the individual variations in the equilibrium plasma quinacrine levels are expressed logarithmically the distribution is approximately symmetric and is found to approach closely a logarithmic probability distribution (chart 14). The normality of the logarithmic distribution is demonstrated by the fact that the cumulative frequency curve plotted on logarithmic probability paper yields an approximately straight line over most of the range (chart 15). This linearity test was applied to every set of group data, and satisfactory straight line plots were obtained in all cases. The few exceptional subjects who exhibited abnormally high quinacrine levels for extended periods were insufficient in number to affect significantly the group values.

The representative value for data which are characterized by a logarithmic probability distribution is the geometric mean, abbreviated to $MEAN_G$. This is the antilog of the arithmetic mean of the logarithms of the observed values and thus differs from the customary arithmetic

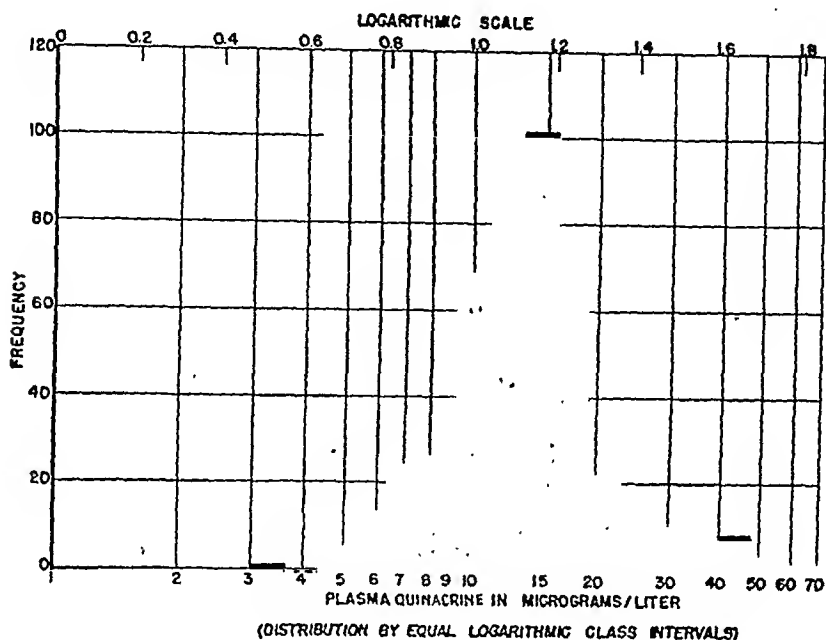


Chart 14.—Frequency distribution of plasma quinacrine levels in Company B, Section 1, seventh through eleventh week.

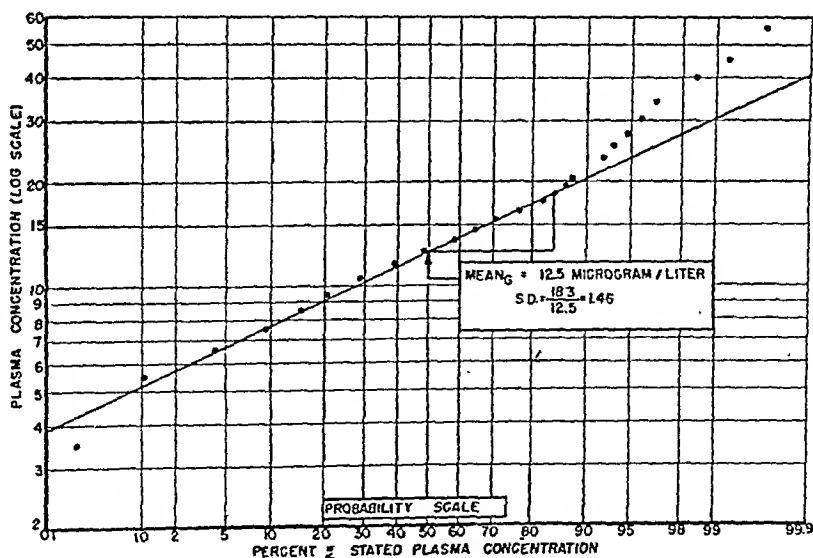


Chart 15.—Cumulative percentage distribution of plasma quinacrine levels in Company B, Section 1, seventh through eleventh week.

mean. The dispersion of logarithmically distributed data is measured by the standard geometric deviation rather than by the standard deviation as in arithmetically distributed values. The standard geometric deviation

tion is the antilog of the standard arithmetic deviation of the logarithms of the observed values about the logarithmic mean. As a measure of the dispersion of data the standard geometric deviation differs basically from the common conception of linear dispersion as measured by the arithmetic standard deviation. In a normal arithmetic distribution the probabilities are equal that deviations of plus or minus 1 standard deviation about the mean will occur. With a log-probability distribution, on the other hand, probabilities are equal that deviations obtained by multiplying or dividing the $MEAN_G$ by 1 standard geometric deviation will occur. Thus, in terms of a normal logarithmic probability curve, the relative significance of high and low values becomes quite different from their meaning when viewed in arithmetic relation to the mean.

TABLE 11.—*Predicted Distribution of Individual Plasma Levels in Men on a Given Regimen (Presented as a Cumulative Frequency Distribution of the Individual Plasma Levels, Which Are Expressed as Ratios of the Mean_G of the Group)*

Individual Levels (Factor by Which Mean _G Is to Be Multiplied)	Percentage of Men Having Stated Level or Less
0.4 × Mean _G	1
0.5	3
0.6	8
0.7	17
0.8	27
1.0	50
1.2	70
1.4	82
1.6	90
2.0	97
2.5	99

Under the geometric concept, a level of 80 micrograms per liter in a group of data having a geometric mean level of 20 micrograms per liter has the same probability of occurrence as a level of 5 micrograms per liter ($\frac{80}{20} = \frac{20}{5} = 4$), whereas in a normal arithmetic probability distribution with an arithmetic mean of 20, values of 5 would occur with much greater frequency than values of 80. It is not suggested that the geometric distribution is an invariable characteristic of the plasma quinacrine levels of a group. It was, however, repeatedly observed in this study and provided a method for describing the variability of the plasma quinacrine levels which was more representative than the common arithmetic method. The standard geometric deviation was found to be almost constant for all sets of data and varied but little from week to week. Its average value of 1.45 permits one to predict (within the limits of the study) the range and distribution of the individual plasma quinacrine levels in a group of men subjected to a given suppressive regimen (table 11).

The dispersion of individual values by 1 standard geometric deviation (68 per cent range) about the geometric mean is shown graphically in charts 3 and 4. The values included within a range of 1 standard geometric deviation on either side of the $MEAN_G$ are also listed in the tables. From these values and the standard error of the means the $MEAN_G$ are shown to be highly stable.

Not evident in either the charts or the tables is the wide variance of certain subjects whose plasma levels fell outside the 68 per cent range. These men were characterized by either consistently low or consistently high values. The high values resulted from a sudden departure from previous levels which, though declining somewhat thereafter, remained elevated above the remainder of the group. In view of the small sample studied, the validity of special consideration for the small numbers of subjects who lie at the extremes may be questioned, since the sample was insufficient to make certain that only one universe was under study. One assumes, nonetheless, that with a sufficiently large sample the discontinuity would be eliminated. The characteristics of the groups at the extremes are worthy of discussion, since they illustrate types of behavior which may be of practical importance from the standpoint of suppressive therapy.

Approximately 7 per cent of both the men receiving 0.4 Gm. per week and the men receiving 0.6 Gm. per week showed unusually low levels for their respective groups. These men reached their equilibrium values earlier than the group as a whole and maintained consistently low levels. This was apparently a characteristic of the individual response to the drug. The low values were not the result of failure to take the drug or of lack of solution of the tablet in the intestine, for the administration of quinacrine in solution produced no change in plasma values.

Another 7 per cent of both the subjects receiving 0.4 Gm. per week and the subjects receiving 0.6 Gm. per week exhibited a more or less sudden departure from previous plasma levels to exceptionally high ones. This rise to unusually high levels was irregular in appearance, occurring at various times between the third and eighth weeks. After the new high level had been reached the behavior varied. In the main there followed a gradual decline to a new level which, nevertheless, was significantly higher than either the level before the sudden rise or the level for the group. These sporadic increases in plasma level were not associated with clinical evidence of toxicity nor with evidence of associated hepatic damage. Typical curves of plasma quinacrine levels illustrating the responses of men with unusually high or unusually low levels are presented in chart 16.

The wide dispersion of values about the mean is a matter of considerable practical importance in any consideration of the degree of

protection afforded a population by any standard dosage regimen. From the point of view of characterizing the population as a whole, the mean and the standard deviation are useful tools. From the point of view of protection of troops in the field, however, it is the status of that portion of the group with the lowest plasma levels which is a matter of concern,

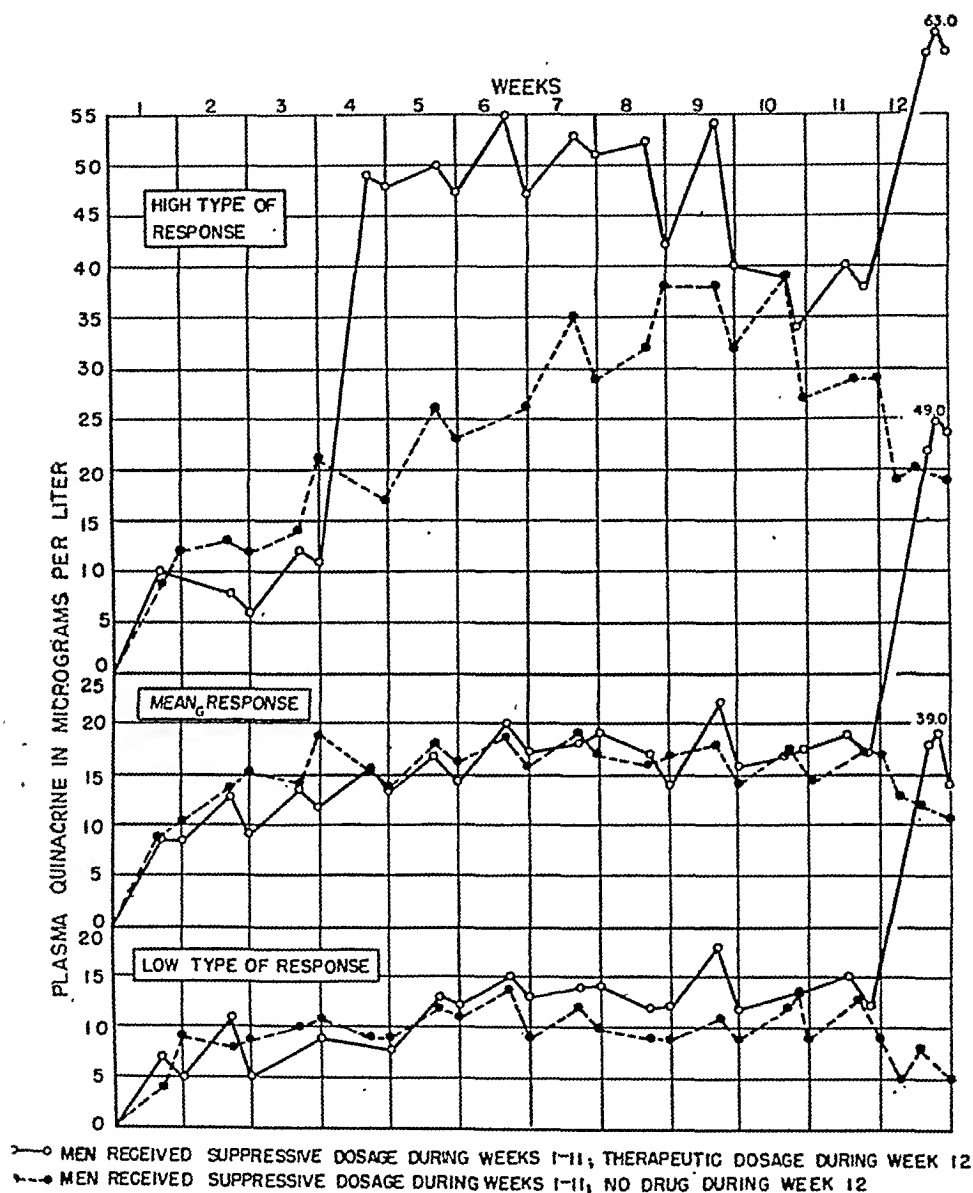


Chart 16.—Differences in plasma quinacrine levels of persons receiving 0.6 Gm. per week.

since it may be assumed, granting the premise that the effectiveness of the drug is a function of the plasma level, that this fraction of the group has the least protection and will manifest the highest malaria attack rate. With this in mind the population may be examined during the different weeks of suppressive dosage to determine what per cent of the total exceeds or fails to achieve any arbitrarily selected plasma level. In charts 17 and 18 the distribution of plasma quinacrine levels

in each week is plotted as a single curve. These are smoothed probability curves obtained from the calculated geometric means and standard geometric deviations of the data.⁸ They represent the most probable prediction curves which emerge from the present study. If, for example, a level of 10 micrograms per liter is desired, one finds that at equilibrium (weeks 7 through 11) 37 per cent of the group receiving 0.4 Gm. per week failed to reach this level (chart 17) whereas only 7 per cent of the group receiving 0.6 Gm. per week were below it (chart 18). It is also apparent, even in the group receiving 0.6 Gm. per week, that the maximum level for the group is not achieved until the seventh week of quinacrine administration.

Prediction of Plasma Quinacrine Concentration.—Lieut. Col. F. S. Brackett, a member of the laboratory staff, developed a mathematical relationship which accurately describes the plasma quinacrine concentration as a function of time and amount of the dose. This mathematical description applies only to group mean levels, but for such means agrees with all the experimentally determined points within the precision of the analytic technic used. The complete development and detailed application of the formulas will be published elsewhere.⁶ Only the principles involved and the simple rules which permit prediction of plasma levels for suppressive regimens are discussed here.

After the administration of quinacrine the concentration of the drug in the plasma exhibits rapid changes associated with the absorption and redistribution of the drug. After twenty-four hours these initial changes have practically disappeared, and the values then observed can be readily correlated. As indicated in the introduction, the initial changes will be called "transients," and the term "underlying level" will be applied to all values found more than twenty-four hours after the administration of any dose. The underlying level may be considered to exist at all times but may be concealed by the presence of the transients during the twenty-four hours following administration of the drug. The present discussion is limited to the correlation of the data on underlying levels. This restricts the present discussion to suppressive regimens, since the transients must be taken into account in the prediction of levels for a therapeutic regimen where the doses are administered at intervals of less than a day.⁹

8. The curve for week 4 (chart 18) was incongruous and has been omitted. Data from which it was derived are unreliable because abnormally high results were obtained for all samples on this day.

9. The transient phenomena are subject to mathematical description as satisfactory as that briefly given here for the underlying levels. The complete development of this aspect of the study and its application to prediction of levels encountered on therapeutic regimens will be described elsewhere.⁶

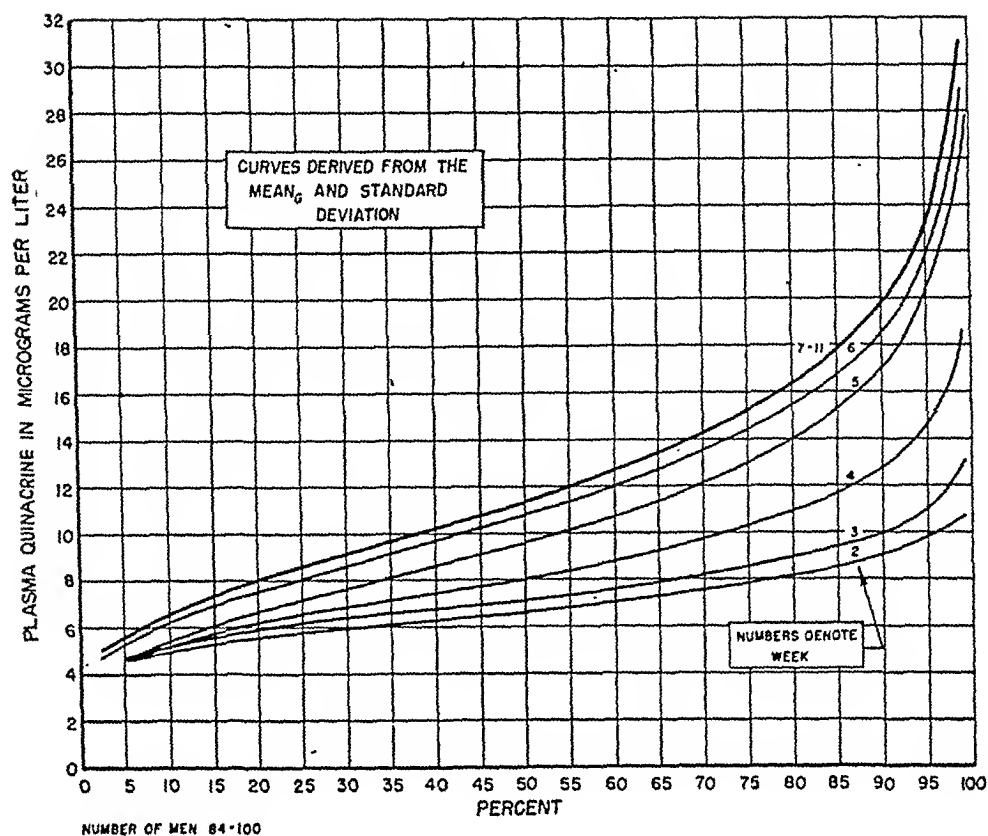


Chart 17.—Cumulative frequencies of minimum weekly plasma quinacrine levels of groups of men (ARTC Companies B and C) receiving 0.4 Gm. per week.

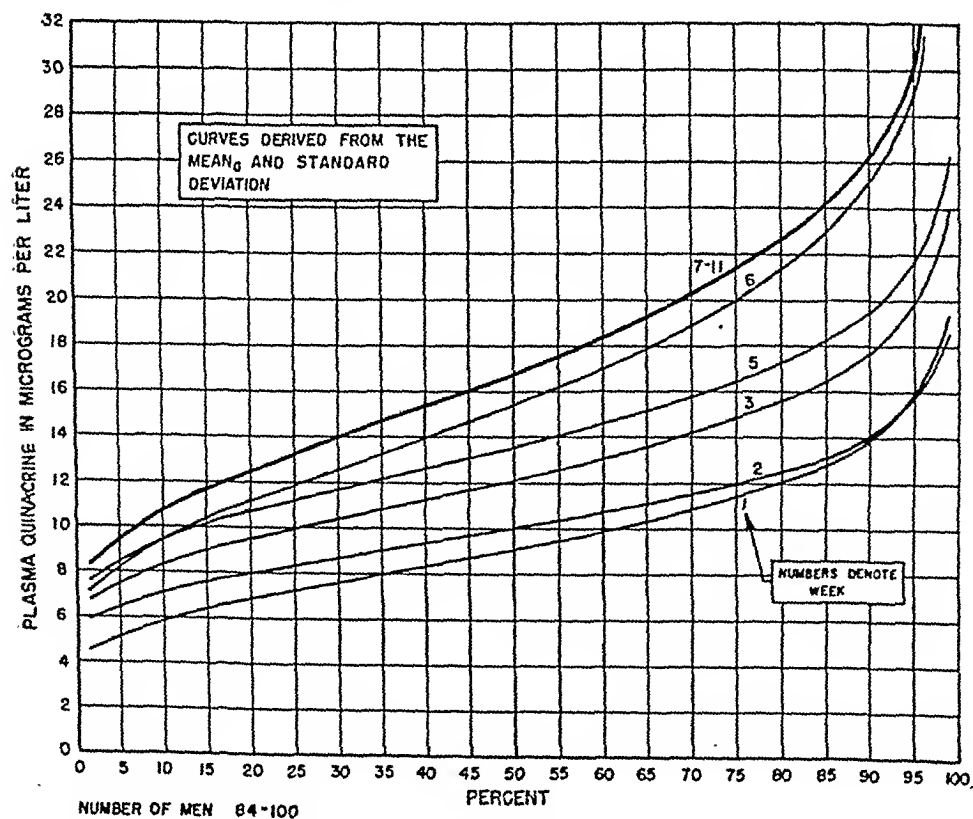


Chart 18.—Cumulative frequencies of minimum weekly plasma quinacrine levels of groups of men (ARTC Companies B and C) receiving 0.6 Gm. per week.

The mathematical analysis indicates that all the observed underlying values can be computed, within experimental error, from two constants. This implies a simple mechanism which may be expressed as follows: The net change in the underlying plasma level is the result of: (1) a gain in concentration directly proportional to the dose—an increase in plasma concentration of 23.2 micrograms per liter per gram of quinacrine hydrochloride ingested—and (2) a loss in concentration proportional to the existing concentration and the time interval—this amounts to 10 per cent of the plasma concentration per day.

These constants lead to a simple rule for predicting the underlying level for any daily dosage regimen, thus: In order to determine the predose level on any day from the predose level of the previous day, the procedure is as follows: (1) To the predose value of the preceding day add the contribution of the new dose, expressed by 23.2 times the daily dose in grams, and (2) from this new value subtract 10 per cent of the new value. This gives the predose plasma quinacrine level in micrograms per liter for the second day.¹⁰

By means of this mathematical approach curves have been built up, day by day, for each of the groups. Chart 19 indicates the excellent agreement of the observed $MEAN_G$ values for a group of 84 to 100 men with the theoretically computed values for the group over a period of eighty-five days. Similar agreement is evident in the values for a group of 30 men who received 1.2 Gm. in the first week and 0.6 Gm. per week thereafter (chart 20). Calculated values are indicated by the solid curve and the observed values by the dotted curve.

Certain facts in regard to the course which a group will follow arise from the two relations postulated above for the simple mechanisms: When quinacrine is administered in equal daily doses, the underlying level rises by diminishing increments to an equilibrium value, while the loss per day becomes larger and larger until at equilibrium the daily loss equals the contribution of the daily dose. The rise is logarithmic, approaching the equilibrium value asymptotically. This rise may

10. This procedure may be expressed algebraically:

$$L' = L + AD - K(L + AD)$$

Where L = group $MEAN_G$ plasma concentration just before a dose.

L' = same for succeeding day.

D = dose in grams.

A = gain per gram of dose, 23.2 micrograms per liter per gram.

K = fraction of level lost per day, 0.10.

Then $L' = (1-K)(L + AD) = 0.9(L + 23.2D)$

(D may be 0 on days of no dose)

The procedure of adding the gain immediately at the time of administration has been adopted arbitrarily for simplicity and partially to offset the greater loss arising from transient elevation of level.

PLASMA QUINACRINE CONCENTRATION

be described as follows: The increase in level per day is 10 per cent of the difference between the daily level and the equilibrium level. Therefore 50 per cent of the rise takes place in one week, 75 per cent

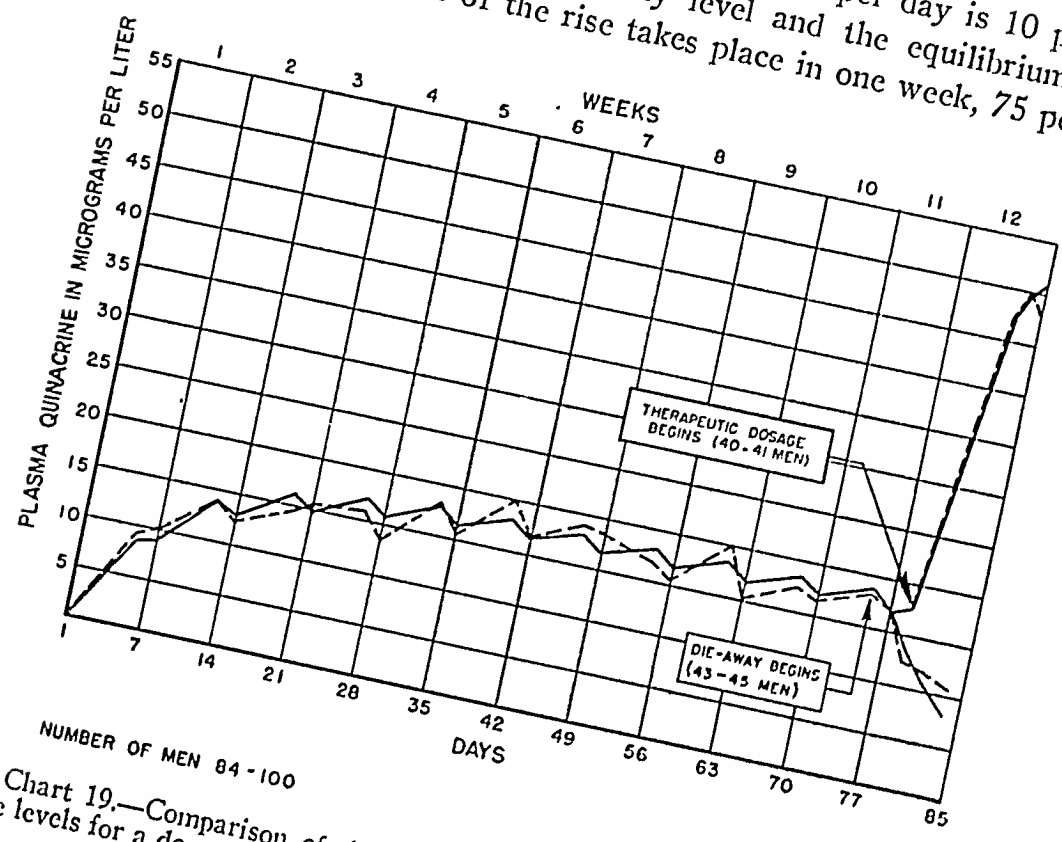


Chart 19.—Comparison of theoretic and experimental MEAN plasma quinacrine levels for a dosage schedule of 0.6 Gm. per week.

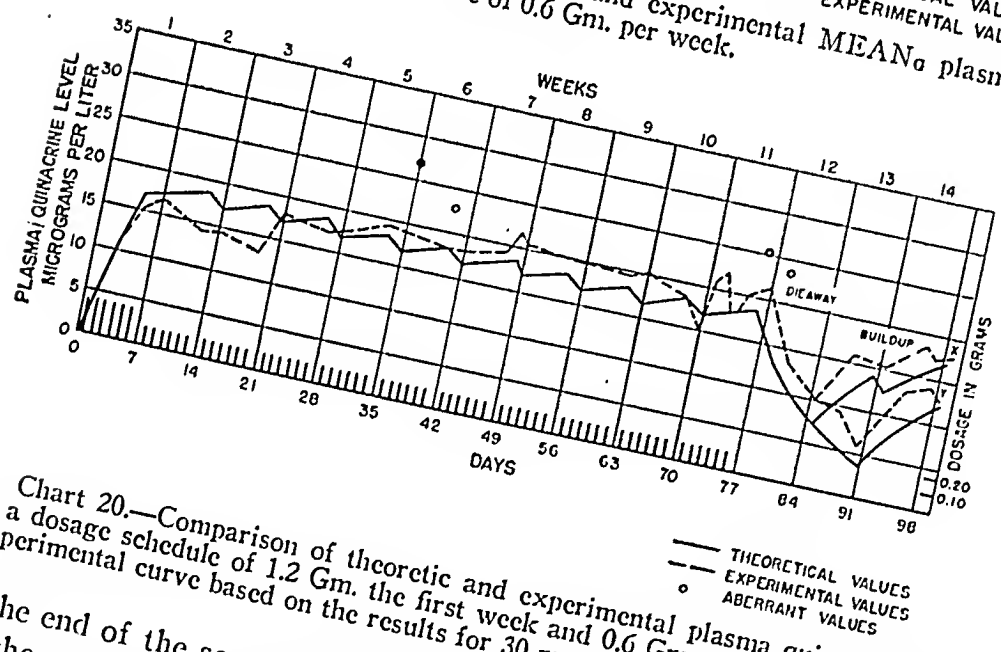


Chart 20.—Comparison of theoretic and experimental plasma quinacrine levels for a dosage schedule of 1.2 Gm. the first week and 0.6 Gm. every subsequent week (experimental curve based on the results for 30 men).

by the end of the second week, 87 per cent by the end of the third, etc. By the end of the sixth week 98 per cent of the rise to equilibrium level has taken place, and only 2 per cent of the total rise remains.

After preliminary training for all subjects, group A entered the hot room while group B remained in the outside summer climate. The men in group A were permitted to leave the hot room from 1 p.m. each Saturday until 10 p.m. Sunday. After seven weeks group A moved outside and group B entered the hot room. For the next four

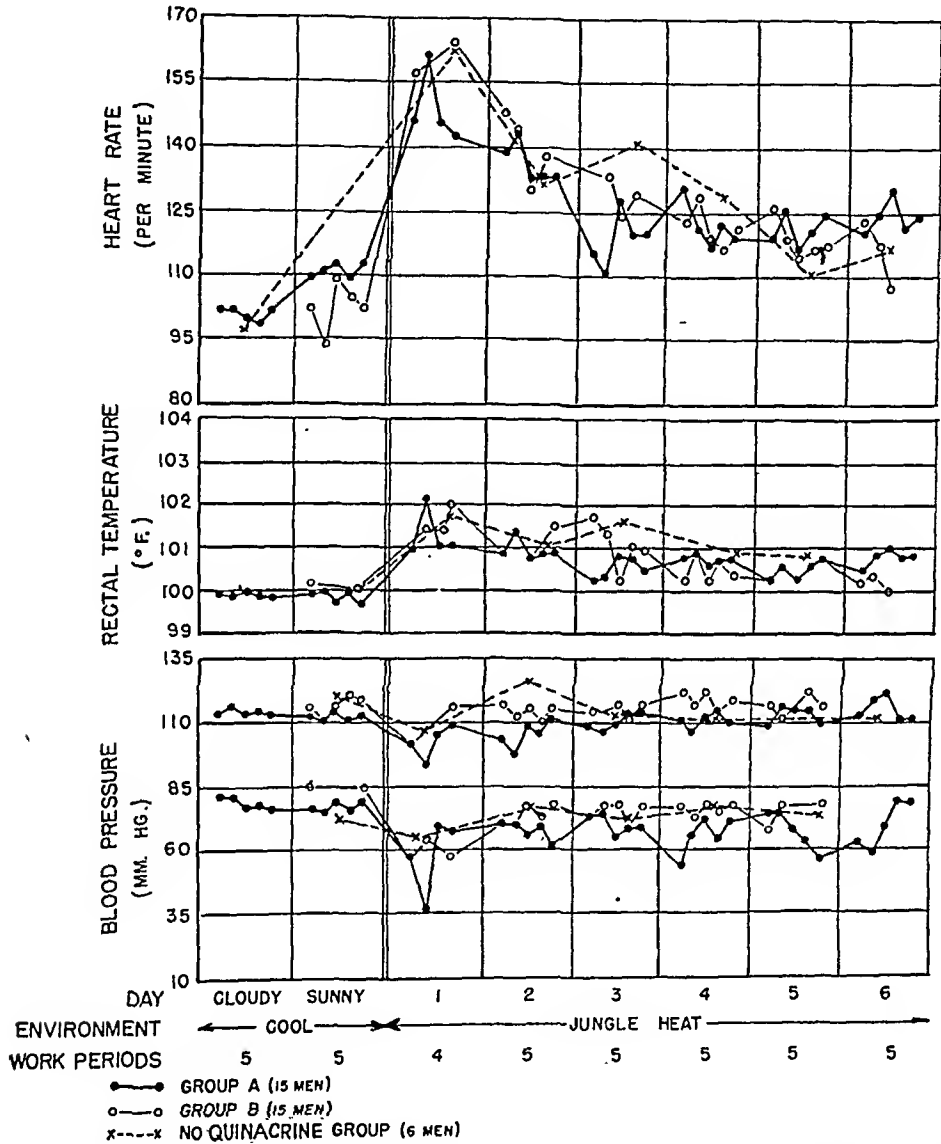


Chart 22.—Changes in heart rate, rectal temperature and blood pressure during acclimatization to work in jungle heat.

weeks group B remained continuously in this environment; they were not permitted to leave on Saturday afternoon and Sunday.

Before and after each work period the following observations were made: (a) general appearance and symptoms, (b) heart rate and blood pressure in both erect and supine positions and (c) rectal temperature. The weight (sweat) loss, within 10 Gm., was determined for each work

period. Measurements of the twenty-four hour water intake and urine output were made daily on the subjects in the hot room.

TABLE 12.—*Mean_G and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Jungle Group A (Receiving 0.6 Gm. per Week)*

No.	Week Date	Number of Men	Mean _G	Bleeding H ₁		Dispersion	
				68% Range of Mean _G	σ_G	68% Range	Mean _A
1	Aug. 12	15	11.6	11.0 - 12.1	1.21	12.1 - 13.9	11.8
2	16	15	18.2	17.5 - 19.0	1.17	15.6 - 21.3	18.4
3	23	15	14.6	13.9 - 15.4	1.22	11.9 - 17.8	15.0
4	30	15	18.7	18.0 - 19.4	1.15	16.2 - 21.5	19.0
5	Sept. 6	15	19.7	18.2 - 21.5	1.39	14.2 - 27.4	20.9
6	13	15	28.6	26.0 - 31.5	1.45	19.8 - 41.4	30.7
7	20	14	16.0	14.5 - 17.7	1.46	11.0 - 23.4	20.1
8	27	15	20.1	18.0 - 22.5	1.55	13.0 - 31.2	22.1
9	Oct. 4	15	19.1	17.4 - 21.0	1.44	13.2 - 27.5	20.6
10	11	15	19.3	17.9 - 20.8	1.34	14.4 - 25.8	20.2
11	18	15	15.2	13.9 - 16.7	1.42	10.8 - 21.5	15.5
12	25	14	20.6	19.0 - 22.3	1.33	15.4 - 27.1	21.4
Bleeding H ₂							
1	Aug. 14	15	16.2	15.4 - 17.0	1.21	13.3 - 19.6	16.4
2	21	14	14.3	13.7 - 15.0	1.18	12.2 - 16.9	14.5
3	28	15	13.6	12.9 - 14.4	1.25	10.9 - 17.1	13.9
4	Sept. 4	15	17.7	16.2 - 19.2	1.39	12.7 - 24.6	18.6
5	11	15	19.4	18.1 - 20.8	1.48	13.1 - 28.8	21.1
6	18	15	21.4	19.6 - 23.3	1.40	15.3 - 30.0	23.9
7	25	15	17.9	16.1 - 19.9	1.49	12.0 - 26.8	19.5
7	26	13	20.8	19.1 - 22.9	1.42	14.7 - 29.7	22.3
8	Oct. 2	15	19.2	17.1 - 21.6	1.57	12.3 - 30.1	21.1
9	9	15	20.7	19.5 - 22.0	1.42	14.5 - 20.1	22.0
10	16	15	21.3	19.6 - 23.1	1.38	15.4 - 29.4	22.7
11	19	14	20.1	18.8 - 21.5	1.29	15.6 - 25.8	20.7
11	20	14	22.1	20.1 - 24.3	1.42	15.5 - 31.5	23.6
11	21	14	18.0	16.4 - 19.7	1.41	12.7 - 25.8	19.1
11	22	14	18.2	16.8 - 19.8	1.37	13.3 - 24.9	19.0
11	23	14	21.2	19.7 - 22.8	1.31	16.1 - 27.9	22.0
11	24	14	24.4	22.7 - 26.1	1.30	18.7 - 31.8	25.2
12	27	14	21.4	19.9 - 23.0	1.31	16.4 - 28.0	22.1
12	29	13	12.7	11.4 - 14.1	1.47	8.7 - 18.6	13.5
13	Nov. 1	14	8.7	7.9 - 9.6	1.42	6.1 - 12.3	9.2
Bleeding H ₂ + 5							
1	Aug. 14	15	25.2	23.9 - 26.6	1.23	20.6 - 30.9	25.7
2	21	15	22.6	21.8 - 23.4	1.15	19.6 - 26.0	22.8
3	28	15	20.8	19.7 - 21.8	1.23	16.9 - 25.4	21.3
4	Sept. 4	15	26.7	25.2 - 28.4	1.26	21.3 - 33.6	27.5
5	11	15	34.8	32.3 - 37.6	1.34	26.0 - 46.7	36.4
6	18	15	36.6	33.7 - 39.8	1.37	26.7 - 50.4	38.7
8	Oct. 2	15	28.1	26.1 - 30.2	1.33	21.0 - 37.3	29.3
9	9	15	22.8	21.0 - 27.7	1.37	16.6 - 31.2	23.9
10	16	14	24.0	22.1 - 26.2	1.38	17.4 - 33.2	25.2

Blood samples for plasma quinacrine were taken three times each week (a) H₁ at 11:15 a.m. Monday, approximately fifty-four hours after the last preceding dose; (b) H₂ at 6:30 a.m. Saturday, eighteen

hours after the last preceding dose, and (c) H_{2+5} at 11:30 a.m. Saturday, five hours after the last dose of quinacrine of the week. Blood samples were always obtained from both groups at the same time.

TABLE 13.—*Mean_G and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Jungle Group B (Receiving 0.6 Gm. per Week)*

Week		Number Of Men	Bleeding H_1		Dispersion		
No.	Date		Mean _G	68% Range of Mean _G	σ_G	68% Range	Mean _A
1	Aug. 12	15	11.2	10.5 - 12.1	1.32	8.5 - 14.8	11.6
2	16	14	16.1	15.2 - 17.1	1.25	12.9 - 20.2	16.5
3	23	15	14.9	14.4 - 15.4	1.13	13.1 - 16.9	15.0
4	30	14	17.9	17.3 - 18.6	1.23	14.6 - 22.0	18.2
5	Sept. 6	15	15.7	14.6 - 17.0	1.38	11.7 - 21.2	16.5
6	15	15	25.2	23.7 - 26.6	1.08	19.8 - 32.0	25.8
7	20	15	20.4	18.7 - 22.2	1.39	14.7 - 28.2	21.3
8	27	14	21.6	20.3 - 23.1	1.27	17.1 - 27.4	22.2
9	Oct. 4	15	21.1	19.8 - 22.5	1.28	16.4 - 27.1	21.7
10	11	15	21.4	20.1 - 22.9	1.30	16.4 - 28.0	22.3
11	18	14	14.6	13.6 - 15.7	1.30	11.2 - 19.1	15.0
12	25	14	26.6	21.5 - 23.8	1.21	18.6 - 27.4	23.0
Bleeding H_2							
1	Aug. 14	15	16.0	15.1 - 17.0	1.26	12.7 - 20.2	16.4
2	21	14	14.3	13.7 - 14.9	1.16	12.3 - 16.6	14.4
3	28	15	13.4	12.6 - 14.2	1.26	10.6 - 16.9	13.7
4	Sept. 4	15	16.6	14.9 - 18.4	1.50	11.0 - 24.9	16.8
5	11	15	19.6	18.5 - 20.9	1.27	15.5 - 25.0	20.2
6	18	15	24.0	22.5 - 25.7	1.29	18.7 - 30.9	24.7
7	25	15	21.0	19.3 - 22.9	1.39	15.1 - 29.3	22.1
7	26	15	21.5	19.9 - 23.3	1.36	15.9 - 29.2	22.5
8	Oct. 2	15	21.2	19.9 - 22.5	1.27	16.6 - 26.9	21.7
9	9	14	18.4	17.2 - 19.7	1.28	14.3 - 23.6	18.9
10	16	13	15.6	14.5 - 16.8	1.31	11.9 - 20.4	16.2
11	19	15	22.2	21.0 - 23.3	1.22	18.1 - 27.1	22.6
11	20	15	22.6	21.3 - 23.9	1.25	18.0 - 28.2	23.1
11	21	15	19.1	18.1 - 20.2	1.23	15.5 - 23.5	19.5
11	22	15	17.8	16.4 - 19.3	1.35	13.0 - 24.3	22.1
11	23	15	19.4	18.3 - 20.6	1.27	15.4 - 24.6	19.9
11	24	15	26.0	24.5 - 27.5	1.25	20.8 - 32.4	26.5
12	27	13	25.9	24.1 - 27.8	1.29	20.0 - 33.5	26.6
12	29	14	13.7	12.8 - 14.6	1.28	10.7 - 17.5	14.1
13	Nov. 1	14	11.1	10.1 - 12.2	1.44	7.7 - 16.0	11.7
Bleeding $H_2 + 5$							
1	Aug. 14	15	25.6	24.3 - 26.9	1.22	21.0 - 31.1	26.1
2	21	15	20.1	19.4 - 20.7	1.14	17.6 - 22.8	20.2
3	28	15	19.2	18.4 - 20.0	1.17	16.4 - 22.4	19.4
4	Sept. 4	15	24.2	23.2 - 25.2	1.17	20.7 - 28.2	24.5
5	11	14	29.7	28.5 - 31.0	1.17	25.4 - 34.7	30.4
6	18	15	33.5	31.2 - 35.9	1.31	25.6 - 43.8	34.6
8	Oct. 2	15	26.8	25.0 - 28.6	1.30	20.6 - 34.8	27.6
9	9	10	22.7	21.9 - 24.1	1.21	18.8 - 27.5	23.1
10	16	15	22.3	21.3 - 23.3	1.19	18.8 - 26.5	22.7

Results.—In chart 22 are compared the work performance and rate of acclimatization in humid heat of three groups of men: (a) group A,

men receiving quinacrine daily simultaneously with entry into the hot environment; (b) group B, men who had received quinacrine for seven weeks before exposure to the hot environment, and (c) a control group

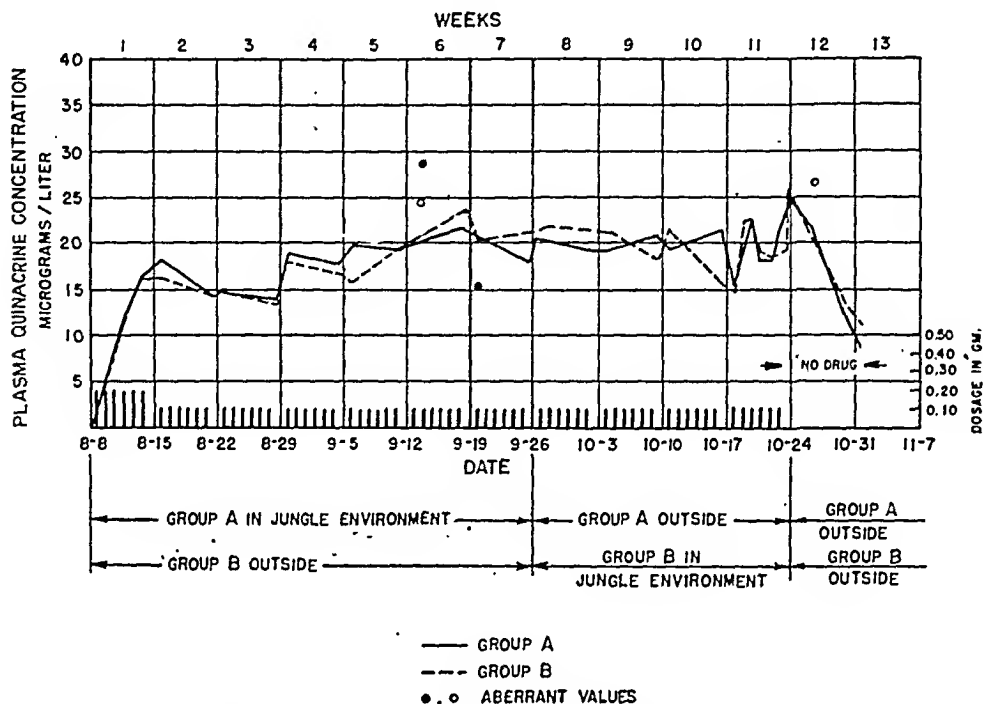


Chart 23.—MEAN plasma quinacrine concentrations of jungle groups A and B.

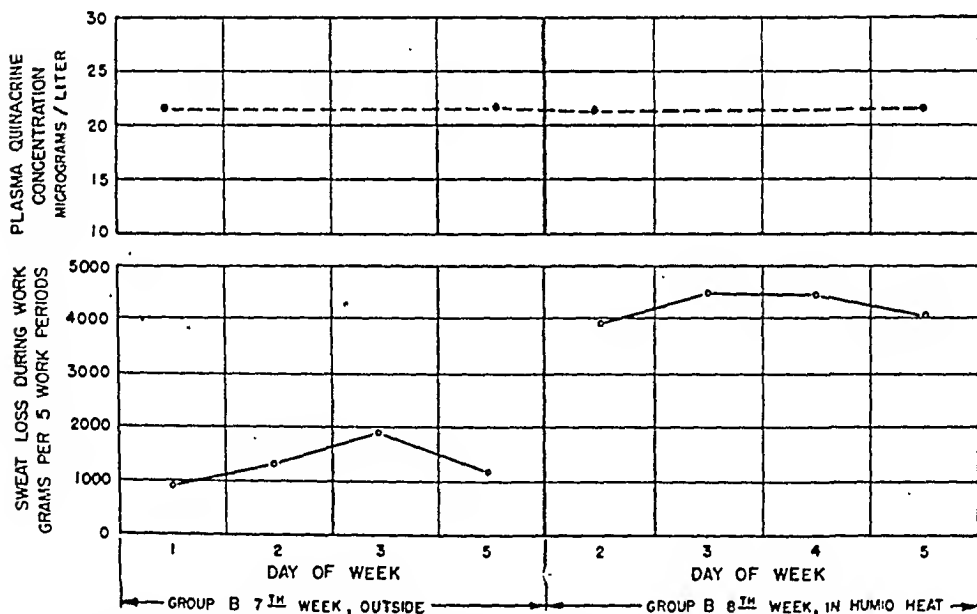


Chart 24.—High rate of sweat loss in humid heat does not affect plasma quinacrine concentration.

of 6 men who received no quinacrine at any time. The performance on the first day and thereafter and the progress of acclimatization in the three groups of subjects did not differ in any significant way from

that observed in previously reported studies of the effect of moist heat on the performance of men.¹¹ With or without quinacrine the rate of acclimatization and ability to work in a jungle climate were the same.

As shown in chart 23 there was no difference in the rate of increase of the plasma quinacrine concentration or in the final equilibrium levels attained in groups A and B, nor was there a significant change in the equilibrium level in either group when the subjects were shifted from one environment to the other (group data tabulated in tables 12 and 13). The increased rate of sweating experienced by the men in the hot humid environment had no effect on the plasma quinacrine level (chart 24).

The equilibrium levels attained by these two groups (A and B) and the levels reached by the larger ARTC group on the same weekly maintenance dosage did not differ significantly from the level of 18 micrograms per liter predicted for this dosage schedule, the deviations being

TABLE 14.—*Equilibrium Quinacrine Level on Dosage of 0.6 Gm. per Week; Mean_G and Dispersion of Levels*

Exposure	No. of Results	No. of Men	Levels Seventh Through Eleventh Weeks		
			Mean _G	S. E. of Mean _G	Std. Geom. Deviation
Outside, ARTC group.....	858	85	17.2	1.04	1.44
7 wks. hot room, 4 wks. outside, group A.....	205	15	19.9	1.17	1.41
7 wks. outside, 4 wks. hot room, group B.....	205	15	19.9	1.08	1.32

approximately equivalent to one standard error of the mean. This is apparent in table 14.

The mean levels and the degree of individual variability as measured by the standard deviations are approximately the same for the three groups. Both groups A and B had men with unusually low and unusually high levels.

It is concluded, therefore, that the hot, humid environment has no effect on the absorption and storage of quinacrine and that the required dosage schedule for effective plasma quinacrine concentration is not influenced by the climatic conditions here studied.

VI. THE TOXICITY OF QUINACRINE

There were no toxic reactions attributable to quinacrine in any of the 250 men on any of the suppressive dosage regimens. The health and well-being of all the men were excellent throughout. The ARTC group

11. Eichna, L. W.; Bean, W. B.; Ashe, W. F., and Nelson, N.: Bull. Johns Hopkins Hosp. 76:25, 1945; Armored Medical Research Laboratory Report on Project 2 (2-7, 11, 13, 15, 17, 19), Oct. 18, 1943.

gained in weight an average of 3 pounds (1.3 Kg.) during the experimental period. Visits to the dispensary by all men in the study were carefully checked. In no instance could the complaints be attributed to quinacrine, nor was the frequency of visits by members of the experimental groups greater than that of other men in the same unit who were not taking the drug.

One instance of probable toxic reaction from quinacrine in therapeutic doses was encountered. This subject had an epileptiform seizure on the fifth day of therapeutic dosage. He had never had a previous seizure, and he had manifested no disturbance while taking suppressive doses. On the day following the seizure his plasma quinacrine level was 108 micrograms per liter, the highest attained by any subject on the therapeutic regimen. Forty-eight hours after the seizure the plasma level had fallen to 67 micrograms. The administration of the drug was continued throughout the seven day regimen, and no further incident occurred. The groups exposed to the hot humid environment remained well throughout.

In view of the frequent reports of quinacrine toxicity the failure to encounter toxic manifestations during the suppressive dosage regimens of the present study is of interest. The subjects of this study differed from men in combat theaters in the absence of the psychologic stresses of combat. In the presence of such stresses one may properly question whether the drug when administered in accordance with the schedule recommended can be considered solely responsible for the reported complaints.

The characteristic yellow discoloration from the drug was noticeable by the end of the first month and increased progressively thereafter. Neither the intensity of this color nor the fluorescence of skin and nails under ultraviolet light correlated with the plasma quinacrine levels.

SUMMARY

1. *Absorption of Quinacrine Following a Single Dose.*—After oral ingestion of quinacrine hydrochloride (atabrine) the plasma level rises rapidly. The major portion of this rise occurs in two hours, and the peak is reached within eight hours. The decrease is rapid at first but becomes progressively slower. By the end of twenty-four hours the rate of fall has assumed a uniform rate proportional to the plasma level. The form of this postabsorption curve changes with continued intake.

2. *Build-Up of Plasma Quinacrine Concentration.*—On a given dosage regimen the plasma concentration increases rapidly during the first week and then more slowly as equilibrium is approached. At the end of the first week approximately one half of the final equilibrium level is attained, at the end of the second week three fourths of the equilib-

rium level, at the end of the third week 87 per cent, at the end of the fourth week 94 per cent and so on, each week halving the remaining difference, so that by the end of the sixth week no perceptible difference from the equilibrium level is observed.

3. *Equilibrium Level Attained in Relation to Dosage Regimen.*—At equilibrium the average plasma quinacrine concentration depends on the total weekly dose and is directly proportional to this dose. Thus for the two regimens, 0.4 Gm. per week and 0.6 Gm. per week, the group mean equilibrium levels attained were 12 and 17 micrograms per liter respectively. In view of this direct proportionality it is possible, within the general limits of the study, to predict the equilibrium plasma level for other dosage regimens. The relationship is : 30 micrograms per liter for 1 Gm. weekly dose.

4. *Effect of Large Initial Doses on the Time Required to Reach Maintenance Levels.*—On a regular regimen of quinacrine intake, from four to six weeks are required to attain the final equilibrium levels. Since half equilibrium values are reached with any regimen in one week, doubling the maintenance dosage for a first week will produce at the end of this time the same level as the equilibrium level of the maintenance dose. This avoids from three to five weeks of delay.

5. *Plasma Levels Attained with the Therapeutic Dosage Schedule.*—Individuals within a group roughly tend to maintain the same distribution of levels on a therapeutic regimen as they exhibited on a suppressive regimen. However, the correlation is not high. The increase of plasma concentration with the institution of a therapeutic regimen after the establishment of equilibrium under a suppressive dosage schedule is functionally related to the time and amount of dose in the same way as at lower and slower rates of intake.

6. *Decrease of Plasma Quinacrine Concentration After Discontinuing the Drug.*—When the drug is discontinued after the establishment of equilibrium levels, the plasma quinacrine concentration decreases in a manner similar to the initial build-up. Thus, 10 per cent of the remaining level is lost each day, and at the end of a week the level will have dropped to half the equilibrium value, to one fourth in two weeks, one eighth in three weeks and so on, each week halving the remaining concentration.

7. *Individual Variability.*—The difference between plasma levels in different individuals may be great. This variability follows a regular pattern and is consistent with the type of statistical analysis (geometric) to which the data have been subjected.

8. *Effect of Climatic Environment on Equilibrium Level.*—In a hot humid environment producing copious sweating the course of build-up and the equilibrium level attained with a given regimen of quinacrine

were the same as those with the same dosage schedule in a temperate climate. Climate had no influence on the equilibrium plasma quinacrine level.

9. *Toxicity*.—There were no toxic reactions from quinacrine in any of the subjects on the various suppressive regimens. One instance of probable reaction to therapeutic dosage occurred.

The following enlisted technicians assisted in these studies: Corporal Alexander Adler, Technician Third Grade Ralph J. Bloom, Sergeant Walter C. Davies, Technician Third Grade Kenneth C. Davis, Sergeant Ernesto Ferrer Jr., Technical Sergeant Eli Gold, Technical Sergeant John L. Gray, Technician Fourth Grade Wayland James, Sergeant Melvin H. Kaplan, Technician Third Grade Arthur Kunes, Technician Fourth Grade Alvin Lieberman, Technician Fourth Grade Guy Millikan, Technician Third Grade Max E. Ress, Technician Third Grade Edward M. Shottick, Master Sergeant Theodore C. Swigert and Technician Fourth Grade Felix Urbush.

Progress in Internal Medicine

ALLERGY

A Review of the Literature of 1944 and 1945, with Comments on Future Problems

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(Concluded from Page 718)

HAY FEVER

There are two parts to the treatment of hay fever. One concerns the choice of the particular extract to be used in treatment; the other concerns the technic of doses.

The choice of extracts is important, and, as usual, it is the history which gives the best clue. Skin tests are always interesting, but when one can demonstrate many skin tests with positive reactions that have no symptoms to go with them and then can find clinical evidence of sensitiveness in spite of skin tests with negative reactions one learns to recognize the limitations of the method.

Around Boston, for example, one can distinguish two varieties of what used to be called the typical ragweed history. In one group of patients, the symptoms of hay fever begin around the middle of August, the peak of symptoms is near the first of September and then the symptoms subside, to leave the patient quite clear by about September 20. In the other group of cases the onset is a little earlier, perhaps toward the middle of August, and then the symptoms persist, to recur in paroxysms through October. This type of hay fever comes later than the type caused by ragweed. Patients who give that history often have positive cutaneous reactions to molds, and if extracts of these molds are used in treatment along with ragweed the results are improved. For some reason, molds appear to be more important for treatment of children than they are for treatment of adults.

It is necessary to know much more about the molds. The trouble is that the study is immensely difficult. Once more I have to call attention to an observation which was made in the allergy clinic of the Massachusetts General Hospital in 1938.⁶² A plant pathologist engaged in the study of the fungous disease which injures tomato plants acquired sensitiveness to the mold *Cladosporium fulvum* Smith. Skin tests with

62. Rackemann, F. M.; Randolph, T. G., and Guba, E. F.: The Specificity of Fungous Allergy, *J. Allergy* 9:447, 1938.

the extracts of this mold gave positive reactions. At the same time other tests were made, closely related species of the *Cladosporium* genus being used, and it was found that whereas the patient showed slight reactions to these other species the degree of sensitiveness was much smaller. Here then was evidence of a strict specificity not only to a genus of molds but to a particular species within that genus. My colleagues and I treat our patients with an extract of a stock culture of the mold *Alternaria* or perhaps *Hormodendrum* or *Aspergillus*, and occasionally the results are good. Is it not possible that with better methods of selection of the molds to be used our results might be much better? Studies of the incidence of air-borne molds show a tremendous number of varieties and species, with a predominance of this or that mold depending on factors which are not clear. Harsh and Allen⁶³ studied the fungous contaminants of the air of San Diego, Calif., and pointed out that the count of molds which grew on exposed nutrient plates was quite different from the count of mold spores which fell on greased slides. In another paper Harsh⁶⁴ proposed a mathematical formula for determining the importance of any one species. From Brazil has come a report on air-borne molds by Passarelli and others.⁶⁵ A good review of the literature on molds is one by Morrow and Lowe.⁶⁶

On pollens, too, more study is needed to determine the actual specificity of the different varieties or, on the other hand, to show that there is enough crossed relationship between these species to justify the present comfortable conclusion that treatment with one or two of the common grasses, for example, is enough "to take care of" all the grasses at the same time. Chobot and Dundy⁶⁷ have sought for the cause of hay fever which occurs between the grass and the ragweed season in New England. Skin tests were made with a variety of odd and unusual pollens, and a number of positive reactions were observed, but on account of the discrepancy between skin tests and history these reactions did not help much in the evaluation of the importance of any one pollen. At the present time, there are only two crude methods of selection. One is the history, to indicate the dates as accurately as possible. The other is a field survey augmented by pollen slides to

63. Harsh, G. F., and Allen, S. E.: A Study of Fungus Contaminants of the Air of San Diego and Vicinity, *J. Allergy* **16**:125, 1945.

64. Harsh, G. F.: Pollinosis in San Diego County, California, with a Proposed Method for the Estimation of the Relative Importance of the Plants Concerned, *Ann. Allergy* **3**:27, 1945.

65. Passarelli, N.; de Miranda, M. P., and de Castro, C.: Mold Studies in Rio de Janeiro, *Rev. med.-cir. do Brasil* **52**:173, 1944.

66. Morrow, M. B., and Lowe, E. P.: Molds in Relation to Asthma and Vasomotor Rhinitis, *Mycologia* **35**:638, 1943.

67. Chobot, R., and Dundy, H. D.: The Causes of Hay Fever Occurring Between the Grass and Ragweed Season, *J. Allergy* **15**:182, 1944.

make sure that the suspicion about any particular plant can be supported by showing that it is capable of producing pollen in reasonable quantity and that the particular patient has probably been exposed to it.

As for surveys of pollen, it is interesting to have Greco⁶⁸ state that in Brazil the grasses are the chief offenders and that the pollenating season occurs from the middle of May to the end of June. This is surprising because in the southern latitudes May and June would correspond to November and December in the northern latitudes; it would be the fall rather than the spring season.

The mechanism of hay fever and the technic of specific treatment are problems of primary importance, because pollen sensitiveness is the simplest form of allergy and it concerns thousands of patients who suffer. In 1935, Cooke, Barnard, Hebal and Stull⁶⁹ first presented evidence for an antibody in hay fever which could block the union of ragweed with the ordinary sensitizing antibody called reagin. Since then, the study of this blocking antibody has been continued by Loveless.⁷⁰ She has developed a technic for measuring the amount of this blocking antibody, and she can show that the amount is proportional to the degree of improvement in symptoms following treatment. There are two kinds of antibodies in hay fever. The sensitizing antibody is thermolabile, destroyed by heating to 56 C., while the blocking antibody is thermostabile and resistant to heat for a long time. If there are two antibodies then there must be two separate antigens, and this fits in with the conclusions which Newell⁷¹ reached in 1942, that it was impossible to purify the extract of ragweed by physical means. All the different fractions which he could separate by precipitation with ammonium sulfate or with alcohol gave positive reactions in skin tests on patients sensitive to ragweed.

Whether the concentration of the thermostabile antibody is always proportional to the degree of clinical relief from symptoms of hay fever is still debatable. Loveless⁷² said that it is. Cooke,⁷³ however, found

68. Greco, J. B.: Pollen Studies in Brazil: Pollen Counts in Eleven Brazilian Cities, *Rev. med.-cir. do Brasil* **52**:95, 1944.

69. Cooke, R. A.; Barnard, J. H.; Hebal, S., and Stull, A.: Serological Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy (Hay Fever), *J. Exper. Med.* **62**:733, 1935.

70. Loveless, M. H.: Immunological Studies of Pollinosis: I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients, *J. Immunol.* **38**:25, 1940.

71. Newell, J. M.: A Review of Chemical Studies on the Allergens in Pollens, *J. Allergy* **13**:177, 1942.

72. Loveless, M. H.: Immunologic Studies of Pollinosis: VI. Shortening the Treatment of Hay Fever, *J. Allergy* **15**:311, 1944.

73. Cooke, R. A.: A Consideration of Some Allergy Problems: II. Serologic Studies of the Skin-Reacting Allergies (Hay Fever Type), *J. Allergy* **15**:212, 1944.

that it is not. Gelfand and Frank⁷⁴ studied 34 cases. High antibody titers did not always go with high total dosage, and then, more important, high titers were not accompanied with good clinical results in every case. Cohen and Friedman⁷⁵ treated normal persons with a 10 per cent extract of ragweed in repeated doses and then collected their serum globulin, which was found to contain considerable quantities of the thermostabile blocking antibody. To this globulin was added amounts of ragweed extract sufficient to combine completely with the antibody, and then patients were treated with this neutralized antigen. A rise in the titer of the thermostabile antibody was produced. In a discussion of this paper, Loveless noted that the neutralized antigen had produced local and general reactions, showing that the combination was not too stable. It was, however, capable of exciting production of the antibody, but the end results in 31 patients were no better or worse than was the ordinary treatment with ragweed extract by itself. The method is a little different from that of mixing the patient's own sensitive serum with ragweed extract so as to neutralize the skin-sensitizing antibody and then giving the mixture back again. Tuft⁷⁶ said that he tried this and the results were disappointing. To me it would seem like an interesting experiment, and it might be worth trying again. Incidentally, Johnson and her associates⁷⁷ in Alexander's laboratory have with a special technic demonstrated the formation of a precipitate when ragweed extract was added to the serum of treated patients, and the fact supports the antibody theory.

Rhinorrhea Due to Chronic Vasomotor Rhinitis.—"Perennial hay fever" is a troublesome disease, which may be serious. It is included in the conditions dependent on the asthmatic state chiefly because it is associated with other and more typical manifestations and partly because it has eosinophile cells in the nasal secretion. There are two interesting facts about it. One is that when it occurs in young women in their twenties or early thirties and becomes severe it may develop into asthma, which thereupon becomes persistent and severe and may be fatal. This appears to be almost a separate disease, and it deserves much more study. I hope that if others find cases they will report them.

74. Gelfand, H. H., and Frank, D. E.: Studies on the Blocking Antibody in Serum of Ragweed-Treated Patients: II. Its Relation to Clinical Results, *J. Allergy* **15**:332, 1944.

75. Cohen, M. B., and Friedman, J.: Treatment of Ragweed Pollinosis with Antigen-Antibody Mixtures: Preliminary Report, *J. Allergy* **16**:121, 1945.

76. Tuft, L.: Critical Evaluation of Skin Tests in Allergy Diagnosis, *J. Allergy* **14**:355, 1943.

77. Johnson, M. C.; Alexander, H. L.; Robinson, R., and Alexander, J. H.: A Quantitative Method for Measurement of Precipitin Reactions, *J. Allergy* **15**: 83, 1944.

The second fact is that treatment by the use of local drops to the nose may do more harm than good. In particular, the drug called Privine (2-naphthyl-1-methylimidazoline hydrochloride) is especially vicious. At first the effect seems to be "wonderful," but soon the patient and the doctor find that the more is used the more is needed. In 1943 Fabricant and Van Alyea⁷⁸ advised it, and, in 1944, Craver, Chase and Yonkman⁷⁹ described its action. In their book (1944) Feinberg and Durham⁸⁰ recommended Privine, but now Feinberg and Friedlaender⁸¹ have recognized its dangers. Since then, Thomas⁸² has also called attention to the harmful effects of Privine, and I, too, have "cured" several patients by insisting that they abstain from nose drops of every kind. The reason for the trouble with Privine is not yet clear. Skin tests are not helpful.

ASTHMA

When asthma of any kind becomes severe it is apt to be associated with an increase in the white cell count and particularly in the eosinophile cells. One has learned to regard eosinophilia as of bad prognostic import, for apparently it occurs especially in the cases of severe asthma. In 1939 Rackemann and Greene⁸³ presented 8 cases of periarteritis nodosa which had occurred in patients with severe asthma. Since then other patients have been suspected of having the same condition, although their symptoms were not so definite; the diagnosis could not be proved.

Now come two other diagnoses which deserve study in connection with severe asthma and periarteritis nodosa. Loeffler's syndrome is one, and in the lungs are found transient consolidations, which come and go in patients who have been sick for a number of months with what appears to be a disease of moderate severity, although persistent. At Camp Blanding, in twelve months Wright and Gold⁸⁴ saw 26 cases of Loeffler's syndrome. The patients had blood eosinophilias which

78. Fabricant, N. D., and Van Alyea, O. E.: A Note on the Evaluation of Privine HCl as a Nasal Vasoconstrictor, *Am. J. M. Sc.* **205**:122, 1943.

79. Craver, B. N.; Chase, H. F., and Yonkman, F. F.: Pharmacologic Studies of a New Vasoconstrictor: 2-Naphthyl-(1')-Methyl-Imidazoline Hydrochloride (Privine or Naphthazoline), *J. Pharmacol. & Exper. Therap.* **82**:275, 1944.

80. Feinberg, S. M., and Durham, O. C.: *Allergy in Practice*, Chicago, The Year Book Publishers, Inc., 1944, p. 502.

81. Feinberg, S. M., and Friedlaender, S.: Nasal Congestion from Frequent Use of Privine Hydrochloride, *J. A. M. A.* **128**:1095 (Aug. 11) 1945.

82. Thomas, J. W.: Paper read before the American Academy of Allergy, Chicago, Dec. 10, 1945.

83. Rackemann, F. M., and Greene, J. E.: Periarteritis Nodosa and Asthma, *Tr. A. Am. Physicians* **54**:112, 1939.

84. Wright, D. O., and Gold, E. M.: Loeffler's Syndrome Associated with Creeping Eruption (Cutaneous Helminthiasis), *J. A. M. A.* **128**:1082 (Aug. 11) 1945.

ranged up to 32 per cent, and in the sputum eosinophils constituted 90 per cent of the cells found. In Miller's⁸⁵ case the eosinophilia varied from 60 to 85 per cent during the first two months and then returned to normal after treatment with oxophenarsine hydrochloride. (Note the drug used.) Smith's⁸⁶ patient was a woman (aged 55) whose white cell count was 20,000, with eosinophils 49 per cent. A roentgenogram showed extensive shadows involving the whole right lung, but two weeks later another plate showed the area clear. Jones and Carlton⁸⁷ have discussed such causes as tuberculosis, intestinal parasites, brucellosis and trichinosis, without being able to incriminate any one. Hansen-Pruss and Goodman⁸⁸ observed 6 cases; the diseases were mostly in young persons, and all the patients had high eosinophilias.

Closely related is the condition called "tropical eosinophilia." It was described first by Weingarten,⁸⁹ who had made the diagnosis in India and found that the disease was not uncommon in the tropics. It runs a slow course, and the patients are not too sick. This disease may last for months or years, and asthma is an important feature of the symptoms. Here again is a high white cell count, with eosinophils reaching 70 to 80 per cent. During this year there are a number of new reports on tropical eosinophilia. Emerson⁹⁰ observed a young ensign who had had sinusitis and asthma before the war. In India he was completely well for four and one-half years, and then quite suddenly came asthma again, after a mild infection in his eyelid. His white cell count ranged from 15,000 to 20,000, with eosinophils from 15 to 20 per cent. A hepatic abscess was found and drained, and after that the white cell count rose to 32,500, with eosinophils to 78 per cent. The diagnosis of tropical eosinophilia was made, and treatment with carbarsone, in doses of 0.25 Gm. by mouth twice a day for two periods of ten days each, cured him. Did the asthma depend on his asthmatic background? The case reported by Hirst and McCann⁹¹ was that of another naval officer in whom asthma also developed suddenly while the patient was in the Pacific Area. For a whole year he had asthma off and on until finally he was found to have a white cell count of 15,500, with eosinophils up to 72 per cent. His sputum was loaded

85. Miller, H.: Transitory Lung Infiltrations Accompanied by Eosinophilia, *New England J. Med.* **232**:7, 1945.

86. Smith, J. H.: Loeffler's Syndrome, *South. M. J.* **36**:269, 1943.

87. Jones, S. H., and Carleton, R. S.: Eosinophilic Infiltration of the Lungs (Loeffler's Syndrome), *New England J. Med.* **231**:356, 1944.

88. Hansen-Pruss, O. C., and Goodman, E. G.: Allergic Pulmonary Consolidations, *Ann. Allergy* **2**:85, 1944.

89. Weingarten, R. J.: Tropical Eosinophilia, *Lancet* **1**:103, 1943.

90. Emerson, K.: Tropical Eosinophilia, *U. S. Nav. M. Bull.* **42**:118, 1944.

91. Hirst, W. R., and McCann, W. J.: Tropical Eosinophilia: Report of Case, *U. S. Nav. M. Bull.* **44**:1277, 1945.

with eosinophils. No parasites could be found. The administration of neoarsphenamine by vein, five doses given four days apart, cured him.

Apley and Grant⁹² have put together four conditions: intrinsic asthma, periarteritis nodosa, Loeffler's syndrome and tropical eosinophilia. They have many features in common. They have slow chronic courses, no obvious etiology, asthma in each one—though not asthma in every case of periarteritis nodosa—and eosinophilia. Apley and Grant referred to them as representing the "EP syndrome," which means eosinophilia with pulmonary disease. In tropical eosinophilia, the administration of arsenic in the form of carbarsone by mouth or neoarsphenamine or oxophenarsine hydrochloride by vein is a treatment which is almost specific for the disease. The effect is remarkable, and the patient recovers promptly when arsenic is administered. In the other conditions there has been no such good treatment, but, on the other hand, arsenic has not been tried in these other conditions, at least not in a series of reported cases. Does arsenic have any effect on Loeffler's syndrome or on periarteritis nodosa or even on intrinsic asthma? It would seem proper to try arsenic. In case the drug is not effective in these other conditions, then it would seem proper to distinguish tropical eosinophilia from them. If, on the other hand, arsenic does benefit, then one could enlarge one's concept and regard the four states as variations of the same fundamental disease.

"All is not allergy that wheezes," and one finds more and more recognition of the fact that the cause of asthma may be something which the patient carries with him and that it has nothing to do with sensitiveness to foods or to dusts in the environment. Cohen,⁹³ in discussing the classification, gave no figures, but he stated that the cases are about equally divided between extrinsic and intrinsic asthma. Leopold⁹⁴ studied 200 soldiers returned from overseas because of severe asthma. Most of them had been in the tropics, and the trouble began there. In 69 per cent there was a history of asthma prior to enlistment, and this is further support for the "asthmatic state" described at the beginning of this review. In 88 per cent of Leopold's cases the climate alone, perhaps aggravated by dust or infection, was described as the precipitating factor.

As for diagnosis, Swineford and Weaver⁹⁵ have commented once more on the importance of a good clinical history as well as on the

92. Apley, J., and Grant, G. H.: Tropical Eosinophilia, *Lancet* 1:812, 1945.

93. Cohen, M. B.: Bronchial Asthma: Classification Based on Etiological and Pathological Factors, *Ann. Int. Med.* 20:591, 1944.

94. Leopold, H. C.: Study of Asthmatics Returned from Overseas, *J. Allergy* 16:30, 1945.

95. Swineford, O., and Weaver, W. M.: History Taking in Allergy: An Outline for and a Comparison of Results from Two Hundred Histories and Skin Tests, *Ann. Int. Med.* 20:293, 1944.

discrepancies between history and skin tests, which are so common. Out of 355 patients with positive histories of clinical sensitiveness, only 70 had positive reactions in skin tests to go with the histories. In 285 the reactions to the skin tests remained perfectly negative. In his presidential address before the Society for the Study of Asthma and Allied Conditions, Tuft⁹⁶ also laid stress on the history, in his discussion of the difficulties and the pitfalls in relying too heavily on skin tests. Meantime, Oliveria Lima⁹⁶ has given figures for the results of skin tests made on 5,000 allergic patients. Such items as milk, eggs, wheat, rice, tomato and chocolate elicited reactions in from 10 to 42 per cent of the cases. Pollen and fungi were also frequent positive reactors. One wonders whether figures from other clinics would give anything like the same results.

When one distinguishes between extrinsic and intrinsic asthma, the age of onset is of almost primary importance. When the age of onset is below 30, the chances are that the asthma is due to allergy, that is extrinsic. If the asthma began in childhood, it is almost sure to depend on allergy. When, however, the onset of asthma is after a patient has reached the age of 40, then the chance of allergy is much smaller. The use of this principle may be illustrated by the case reported by Wiseman and McCarthy-Brough.⁹⁷ An old widow, of 78 years, weighing only 75 pounds (34 Kg.), died within fifteen minutes after a skin test had been done by the intradermal method. If it had been appreciated that her asthma had begun in childhood, at the age of 4, more attention might have been paid to the possibility of sensitiveness.

Treatment of Asthma.—Penicillin has been used for treatment of asthma, particularly for that which is thought to be on a basis of bacterial infection. Leopold and Cooke⁹⁸ reported the cases of 2 women. The first received over 1,250,000 units, as a result of which violent urticaria with fever developed with "all of the essential characteristics of serum disease [which] persisted for 6 days." After that the asthma cleared and she was free for three months, but then in October came a new cold and asthma recurred. At that point she was given sulfadiazine for a few days, and after this second treatment she stayed well. The condition of the second woman responded with less violence and more satisfaction. She was given 100,000 units of penicillin every day for ten days, after which her asthma cleared and she remained well during

96. Oliveira Lima, A.: A Statistical Study on the Incidence of Intradermal Tests in Five Thousand Allergic Patients, *Rev. med.-cir. do Brasil* **52**:1, 1944.

97. Wiseman, J. R., and McCarthy-Brough, M. P.: Skin Sensitivity in the Aged: Fatality Following the Intradermal Tests, *J. Allergy* **16**:250, 1945.

98. Leopold, S. S., and Cooke, R. A.: Penicillin in the Treatment of Intractable Bronchial Asthma: A Preliminary Report, *Am. J. M. Sc.* **209**:784, 1945.

the five months of observation. Hampton and his co-workers⁹⁹ treated 9 patients with intrinsic asthma with penicillin, but slight improvement occurred in only 4 of the 9 patients. It is the opinion of Hampton and his colleagues that penicillin was of little or no value and offered no advantage over other types of therapy in the treatment of intrinsic asthma. Schonwald and Deppe¹⁰⁰ treated 86 patients with the broth filtered from a culture of *Penicillium notatum* and caused pronounced improvement in 34 of them. Penicillin does good only when the drug reaches the bacteria and reaches it in sufficient quantity. Vermilye¹⁰¹ had a good idea when he placed a strong solution of sodium penicillin, 25,000 units per cubic centimeter, in a Vaponephrin Nebulizer and then connected the apparatus with an oxygen tank to lead oxygen through the liquid and make the patient inhale all of it. With this method the blood concentration could be maintained up to 0.40 units per cubic centimeter. He found the method useful not only in acute primary infections of the bronchi and lungs but in chronic infections as well. With the fine "Aerosol spray" the penicillin is in fact brought into contact with the organisms and so can be expected to be effective.

Reactions to penicillin are all too common. "Serum disease" has occurred in a number of cases. The patients of Leopold and Cooke⁹⁸ have been mentioned. In Lamb's¹⁰² first patient there developed on the fifth day on the genitals and fingers a vesicular eruption, which coalesced later and became eczematous. His second patient had a similar vesicular eruption on his extremities. It is interesting that in both cases the omission of the penicillin was followed by exfoliation of the eruption and clearance of the itching within twenty-four hours. In the patient described by Price, McNairy and White¹⁰³ asthma and giant hives developed on the twelfth day after intensive treatment of his syphilis with penicillin. The reaction was severe, for asthma recurred on the fifteenth day and the boy was almost dead. However, after treatment with oxygen, epinephrine and 50 per cent dextrose intravenously he recovered promptly and was discharged on the eighteenth

99. Hampton, S. F.; Wine, M. B.; Allen, W.; Thompson, C. S., and Starr, M. P.: The Clinical Use of Penicillin in the Treatment of Intrinsic Asthma, *J. A. M. A.* **127**:1108 (April 28) 1945.

100. Schonwald, P., and Deppe, E. F.: *Penicillium Antibiotic in the Treatment of Intrinsic Allergies*, *Northwest Med.* **44**:10, 1945.

101. Vermilye, H. N.: Aerosol Penicillin in General Practice, *J. A. M. A.* **129**:250 (Sept. 22) 1945.

102. Lamb, J. H.: Allergic Reactions During the Administration of Penicillin, *Arch. Dermat. & Syph.* **52**:93 (Aug.) 1945.

103. Price, D. E.; McNairy, D. J., and White, E. L.: Severe Asthma: Delayed Sensitization to Penicillin, *J. A. M. A.* **128**:183 (May 19) 1945.

day. Lyons¹⁰⁴ found among 209 cases that urticaria appeared in 12 of them (5.7 per cent). It occurred as early as the first day or as late as the fourth week of treatment—quite comparable to the reaction after injection of horse serum. Other types of reaction occur. In a patient of Morris and Downing¹⁰⁵ a bullous dermatitis developed from administration of penicillin.

The possible relation between allergy to the fungus *Penicillium* and reactions to the extract penicillin has been considered by Feinberg.¹⁰⁶ *Penicillium* spores constitute at least 11 per cent of all the fungous spores in the air. Ten patients sensitive to molds were found to give 3 plus reactions to the spores of *Penicillium rubrum* and *Penicillium notatum*, but tests on these same persons with penicillin—the purified extract—elicited a negative reaction. Cormia, Jacobsen and Smith¹⁰⁷ have reported on the reactions to penicillin observed in the treatment of 2,000 soldiers. Mild reactions—mostly transient urticaria—were not uncommon. In only 11 patients out of the 2,000 were the reactions bad enough to require stopping of the treatment.

The sulfonamide drugs have also been used for the treatment of asthma. We ourselves have had some success with the sulfonamide compounds in a few cases. Reactions to the sulfonamide drugs are, however, all too common, and particularly when the drug is used a second time. These reactions vary widely in their character. Drug fever is the common one. Dowling and Lepper¹⁰⁸ found that in 5 per cent of 737 patients fever developed during the second course of treatment. When, however, the particular sulfonamide drug taken in the second course was different from that used in the first course, then in only 3 per cent trouble developed. Disturbances of the blood cells appear to be more characteristic. Thrombocytopenic purpura caused by the sulfonamide drugs has been reported: 3 cases by Gorham and colleagues¹⁰⁹ and 1 case by Meyer.¹¹⁰ In the latter the platelet count

104. Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army, *J. A. M. A.* **123**:1007 (Dec. 18) 1943.

105. Morris, G. E., and Downing, J. G.: Bullous Dermatitis (Dermatitis Medicamentosa) from Penicillin, *J. A. M. A.* **127**:711 (March 24) 1945.

106. Feinberg, S. M.: Penicillin Allergy: On the Probability of Allergic Reactions in Fungus-Sensitive Individuals; Preliminary Experiments, *J. Allergy* **15**:271, 1944.

107. Cormia, F. E.; Jacobsen, L. Y., and Smith, E. L.: Reactions to Penicillin, *Bull. U. S. Army M. Dept.* **4**:694 1945.

108. Dowling, H. F., and Lepper, M. H.: "Drug Fever" Accompanying Second Courses of Sulfathiazole, Sulfadiazine and Sulfapyridine, *Am. J. M. Sc.* **207**:349, 1944.

109. Gorham, L. W.; Propp, S.; Schwind, J. L., and Chinenka, D. R.: Thrombocytopenic Purpura Caused by Sulfonamide Drugs: A Report of Three Cases, *Am. J. M. Sc.* **205**:246, 1943.

110. Meyer, A. H.: Thrombocytopenic Purpura: A Case Caused by Sulfadiazine, *California & West Med.* **60**:99, 1944.

fell to dangerous levels. A good point is made by Rothendler and Vorhaus,¹¹¹ who gave penicillin for prevention of generalized sepsis when the leukocytes were depressed in agranulocytosis.

Cutaneous lesions are also important, and the nature of these varies widely from case to case. Fisher¹¹² from Australia reviewed 100 cases of dermatitis following the local application of sulfanilamide. The rash usually appeared from two to four days after the start of treatment, sometimes not until the eighth to twelfth day, and then it cleared when the drug was withdrawn. Patch tests elicited positive reactions. Frist¹¹³ gave a review of 186 cases of reactions to sulfonamide drugs. Fever and cutaneous eruptions predominated. A lucid and complete discussion of the nature and the mechanism of reactions from certain drugs, particularly the sulfonamide compounds, may be found in a paper by Longcope,¹¹⁴ published in *Medicine* in 1943.

The barbiturates may cause trouble in an occasional case. Potter and Whitacre¹¹⁵ described a patient in whom a chill with fever and generalized erythema developed within a few hours after she had taken 0.1 Gm. of phenobarbital.

Theophylline ethylenediamine (aminophylline) is useful in treatment of severe asthma. It is somewhat effective if given by mouth in doses of 0.2 Gm. four times a day, but much more effective if given by vein in a dose of 0.30 Gm., dissolved in 10 cc. of isotonic solution of sodium chloride. Reactions to theophylline ethylenediamine are not common. Hundreds of injections have been given at the Massachusetts General Hospital, with never any serious difficulty, but we are careful to give the injections slowly. Waldbott¹¹⁶ stated that he has given 20,000 injections, with no trouble at all. However, 3 fatalities have been reported by Merrill.¹¹⁷ Two patients were under treatment for cardiovascular disease and 1 for asthma, and in all 3 death followed immediately after the intravenous administration of theophylline ethylenediamine. The useful method of giving theophylline ethylenediamine

111. Rothendler, H. H., and Vorhaus, M. G.: Penicillin in Thiouracil—Induced Agranulocytosis, *J. A. M. A.* **129**:739 (Nov. 10) 1945.

112. Fisher, B.: Dermatitis Following the Local Application of Sulfanilamide, *M. J. Australia* **2**:449, 1944.

113. Frist, I. F.: Reactions to Sulfonamide Compounds: A Review of One Hundred and Eighty-Six Cases, *War Med.* **5**:150 (March) 1944.

114. Longcope, W. T.: Serum Sickness and Analogous Reactions from Certain Drugs, Particularly the Sulfonamides, *Medicine* **22**:251, 1943.

115. Potter, J. K., and Whitacre, R. J.: Dermatitis Due to Barbiturates: Report of a Case with Associated Anemia, *Ann. Int. Med.* **21**:1041, 1944.

116. Waldbott, G. L.: Emergencies in the Allergist's Practice, *J. A. M. A.* **128**:1205 (Aug. 25) 1945.

117. Merrill, G. A.: Aminophylline Deaths, *J. A. M. A.* **123**:1115 (Dec. 25) 1943.

by rectum was first proposed by Dees,¹¹⁸ who treated 49 adults and 6 children with suppositories containing 0.25 Gm. in theobroma oil and wax. Relief of symptoms occurred within twenty minutes, and many epinephrine-fast patients regained their normal response to epinephrine. Barach¹¹⁹ found that a solution of theophylline ethylenediamine, 0.50 Gm. of the drug dissolved in 20 cc. of water, injected into the rectum through a small catheter is easy and safe.

Demerol (1-methyl-4-phenyl piperidine-4-carboxylic acid), a new synthetic, is said to have good spasmolytic and sedative effects without at the same time disturbing the activity of the respiratory center. However, I am skeptical: I believe that sedative drugs of all sorts must be used with great caution in patients with severe asthma. The risk of lowering the activity of the respiratory center and so allowing the patient to suffocate is very real. Morphine should never, in any circumstances, be used in asthma, and the same principle applies to Demerol and all other drugs related to morphine.

Ethylene disulfonate drew a good deal of attention last year. Theoretically, it is a catalyst concerned with enzyme activity, but the quantity advised—a dilution of 1:10⁻¹⁵—seems absurd. Experiments by Fisk, Small and Foord¹²⁰ have shown it to be of no value in the prevention of anaphylactic shock in guinea pigs.

CONDITIONS RELATED TO ALLERGIES

Rheumatoid arthritis, peptic ulcer, colitis and migraine constitute the last line of the diagram in the chart. These are added because there is so much in common between them and the more regular "asthmatic" symptoms. Rheumatoid arthritis may be allergic in the sense of the delayed inflammatory reaction rather than of the immediate urticarial reaction. Rackemann¹²¹ suggested this in 1933, and Aikawa⁶⁰ has discussed it again now. However, rheumatoid arthritis is not associated with asthma and hay fever: It is not an "asthmatic" disease. Whereas its fundamental mechanism may be similar in principle, it is not the same. Peptic ulcer and colitis are in the line chiefly because Selye¹¹ has described gastric hemorrhage as an incident in the alarm reaction and as a result of treating animals with desoxycorticosterone acetate.

118. Dees, S. C.: The Use of Aminophyllin Rectal Suppositories in the Treatment of Bronchial Asthma, *J. Allergy* **14**:492, 1943.

119. Barach, A. L.: Rectal Instillation of Aminophylline in Intractable Asthma, *J. A. M. A.* **128**:589 (June 23) 1945.

120. Fisk, R. T.; Small, W. S., and Foord, A. G.: The Experimental Use of Ethylene Disulfonate (Allergosil Brand) in the Prevention of Anaphylaxis in Guinea Pigs, *J. Allergy* **15**:9, 1944.

121. Rackemann, F. M.: The Role of Allergy in Arthritis, *New England J. Med.* **208**:1347, 1933.

Migraine has a better "case." Randolph¹²² and Wolf and Unger¹²³ here, as well as Estiu and Dumm¹²⁴ in Brazil, have seen patients with migraine whose symptoms disappeared when particular foods, especially milk, were eliminated from the diet. Such cases are rare. Moreover, headache is not a common accompaniment of hay fever and asthma. Horton and his co-workers⁵¹ have done much to stimulate interest in the relation of the histamine problem to the headache problem. They have been able to relieve a number of patients by treatment of "histaminic cephalalgia" with histamine. Atkinson¹²⁵ has described "red" and "white" headaches according to vasodilatation or vasoconstriction, the former being sensitive to histamine. Also he described the relation between Ménière's disease and migraine in a thoughtful discussion. This year Butler and Thomas¹²⁶ advised treating migraine by injection of histamine intravenously in a dilution made by adding 1 mg. of histamine base (2.75 mg. of histamine acid phosphate) to 500 cc. of isotonic solution of sodium chloride, to be given slowly. Another interesting paper is by Wolff and Torda,¹²⁷ who made studies of the urine before and during the migraine seizure. When the urine was added to a bath containing frog muscle, the muscle contracted greatly with urine passed during the headache but not with urine passed before or after the headache. The other day I saw a patient who suffered from attacks of angioneurotic edema and urticaria of considerable severity. A report on this man showed that in 1930 Dr. George MacKenzie had tested his urine in the Dale apparatus. When urine before the attack was added to the Dale bath, the guinea pig uterus did not react but "there was on two occasions a demonstrable reaction similar to that caused by histamine when the urine passed immediately after an attack was used." Was the urine boiled with acid to destroy such vasodilators as "kallikrein" and adenosine without disturbing the histamine? The technic of these experiments is important. Wolff and Torda quoted Hanke and Koessler¹²⁸ as having been unable to find

122. Randolph, T. G.: Allergic Headache: An Unusual Case of Milk Sensitivity, *J. A. M. A.* **126**:430 (Oct. 14) 1944.

123. Wolf, A. A., and Unger, L.: Migraine Due to Milk: Feeding Tests, *Ann. Int. Med.* **20**:828, 1944.

124. Estiu, M., and Dumm, J. F.: Allergic Headaches, *Rev. med.-cir. do Brasil* **52**:23, 1944.

125. Atkinson, M.: Ménière's Syndrome and Migraine: Observations on a Common Causal Relationship, *Ann. Int. Med.* **18**:797, 1943.

126. Butler, S., and Thomas, W. A.: Intravenous Histamine in the Treatment of Migraine, *J. A. M. A.* **128**:173 (May 19) 1945.

127. Wolff, H. G., and Torda, C.: Experimental Studies on Headache: Pharmacodynamics of Urine Excreted During Migraine Headache and Its Relation to Seventeen-Ketosteroid Content, *J. Clin. Investigation* **22**:853, 1943.

128. Hanke, M. T., and Koessler, K. K.: Studies on Proteinogenery Amines, *J. Biol. Chem.* **43**:521, 1920.

by their colorimetric method histamine in the urine during the headache. When the 17-keto steroids were isolated from the urine passed during the headache they produced a contraction of the muscle, and the finding was interpreted as showing the factors of stress and strain in the disease.

Contact dermatitis is not noted in the diagram and yet it is of considerable practical importance in every allergy clinic. It depends on a sensitiveness which is localized to the skin, sometimes to certain parts of the skin, and which is specific for one out of a great variety and number of offending substances. How does this fit the scheme outlined? Do the persons in whom contact dermatitis develops also have the asthmatic state—the *X*? How many of them gave a history of other allergies at the same time? How many have a family history positive for allergy?

Hall¹²⁹ observed 755 employees in the skin clinic of the Douglas Aircraft Corporation and found 202 with occupational dermatitis which was due to zinc chromate in the paint used. Resins were secondary factors. Lockey¹³⁰ laid stress on resins and described the varieties. Lane and his co-workers¹³¹ found that dermatoses of the hands were the chief complaint of 9 per cent of 475 new patients coming to the skin clinic. In this group occupational dermatoses were not common; there were only a few cases in which the lesions were due to a specific acquired sensitiveness. The authors stated the belief that bacteria were the important factors and that excessive soap and water as well as excessive medicinal treatment was the cause of most of the trouble. Figures were not given; the problem in each case was too complicated. Grolnick, Bowman and Walzer¹³² made an interesting study. They found that when the specific contact dermatitis had subsided a test of the site made by injection of the allergen solution into that skin would result in a wheal formation which was larger than the wheal made at another place on the same patient. This goes along with the description of Lane to indicate that the skin once involved in a contact dermatitis becomes altered in its reaction both to specific and to non-specific stimuli. Soap and irritants of all kinds are bad for it.

Dermatitis caused by poison ivy is all too common. It has been cited as the borderline between allergic and normal persons to show that the differences are more of degree than of kind. There is one

129. Hall, A. F.: Occupational Contact Dermatitis Among Aircraft Workers, *J. A. M. A.* **125**:179 (May 20) 1944.

130. Lockey, S. D.: Contact Dermatitis Resulting from the Manufacture of Synthetic Resins and Methods of Control, *J. Allergy* **15**:188, 1944.

131. Lane, C. G.; Rockwood, E. M.; Sawyer, C. S., and Blank, I. H.: Dermatoses of the Hands, *J. A. M. A.* **128**:987 (Aug. 4) 1945.

132. Grolnick, M.; Bowman, K. L., and Walzer, M.: Response of Contact Dermatitis Sites in Atopic Individuals to Subsequent Stimulation with Specific Wheal-Inducing Atopens, *J. Allergy* **16**:188, 1945.

paper on poison ivy which must be read by every one interested. Stevens¹³³ has made an intelligent review of the entire literature on poison ivy, giving the plain facts concerning the so-called specific treatment. He is not encouraging. Meantime, nothing in these papers or in many others on the same subject is said about the patient who is having the disease. So far, it is my impression that whereas eczema of the "atopic" type—that in children and young adults who have lesions on face and neck and in cubital and popliteal spaces (otherwise called "flexural eczema")—is true to the asthmatic picture contact dermatitis does not belong. Perhaps, however, the distinction depends on degree more than on kind, and when the day comes that the nature of the allergic state (my x) is known and a method of inhibiting it is developed it is probable that even though dermatitis caused by poison ivy and other contact dermatitides do not fit the picture a little treatment for x will do them good.

This review points out that in the development of asthmatic symptoms there are a number of parts or "levels" in the mechanism and that each part is more or less separate from the other. In simple allergy like hay fever, treatment at the middle level of the antigen-antibody reaction itself is the method best known at this time. Even when this treatment is entirely successful for the moment, the person is still allergic: He still has his capacity to develop sensitiveness, and he still has his "asthmatic state." He is "cured" only in the clinical sense, and his cure is only temporary and only relative. If, in the future, more can be known about histamine, how to inhibit its release or how to modify the reaction of the asthmatic person toward histamine, many more patients can be cured but, best of all if the reason for the "asthmatic state" could be understood and if the factor which is inherited by certain persons and which develops in others could be known then the work on allergy would be done.

133. Stevens, F. A.: Status of Poison Ivy Extracts, *J. A. M. A.* **127**:912 (April 7) 1945.

News and Comment

SAMUEL S. FELS FUNDS MEDICAL RESEARCH LABORATORY BECOMES ASSOCIATED WITH TEMPLE UNI- VERSITY SCHOOL OF MEDICINE

An association of the Samuel S. Fels Funds Medical Research Laboratory with the Temple University School of Medicine for research in gastroenterology and internal medicine has been consummated. The Fels Research Laboratory will henceforth be known as the Fels Research Institute of Temple University School of Medicine and will be located in the medical school laboratory building at Broad and Ontario Streets. According to the agreement approved by the representatives of the agencies, the Samuel S. Fels Fund will furnish the laboratory equipment and will finance the research program covering the salaries of members of the staff and the Institute's operating expenses. The Management Committee of the Institute will consist of an equal number of members appointed by the cooperating groups. Members from the Temple University will include: Dr. Robert L. Johnson, President of the University; Dr. William N. Parkinson, Dean of the Temple University School of Medicine; Dr. Charles L. Brown, Head of the Department of Medicine, and Dr. Robert H. Hamilton, Chairman of the Medical School Committee on Research. Members from the Fels Medical Research Laboratory are to be designated by their Board.

Dr. Harry Shay, who has been in charge of the Fels Medical Research Laboratory since its establishment in 1934, will remain as Director of the new institute.

The culmination of the plan just accepted has been made possible through the generosity and foresight of Samuel S. Fels, Philadelphia manufacturer, who has long since had a deep interest in research in many fields. Mr. Fels has had the vision to see the tremendous possibility for improving the well-being of mankind by the application of scientific research technics to human problems.

GENERAL NEWS

Meeting of Mississippi Valley Medical Society.—The eleventh Annual Meeting of the Mississippi Valley Medical Society will be held at the Hotel Jefferson, St. Louis, on September 25, 26 and 27. More than thirty clinical teachers from the leading medical schools will conduct the postgraduate assembly, the entire program of which is planned to appeal to general practitioners. There will be over sixty technical and scientific exhibits, noonday round-table luncheons and a banquet, preceded by a social hour. Dr. Arthur H. Compton, Nobel Prize Laureate and Chancellor of Washington University, will be the principal banquet speaker, together with the presidents of the Illinois, Iowa and Missouri State Medical Societies. All ethical physicians are cordially invited to attend. A detailed program may be obtained from the Secretary, Harold Swanberg, M.D., 209-224 W. C. U. Bldg., Quincy, Ill.

Dr. A. J. Geiger of Yale, Winner 1946 Mississippi Valley Medical Society Essay Contest.—Dr. Arthur J. Geiger, assistant professor of medicine, Yale University School of Medicine, is the winner of the 1946 annual essay contest of the Mississippi Valley Medical Society "for the best unpublished essay on a subject of practical and applicable value to the general practitioner of medicine."

He will receive \$100, a gold medal and a certificate of award. Dr. Geiger's subject was "Penicillin Therapy in Subacute Bacterial Endocarditis."

Second prize was awarded to Dr. F. Steigmann of the University of Illinois for his essay, "The Problem of Jaundice in General Practice," and third prize to Dr. Rutherford T. Johnstone of Los Angeles for his essay, "A Basic Approach to the Diagnosis of the Occupational Diseases."

Mississippi Valley Medical Editors' Association Meetings to be Resumed at St. Louis, September 25.—The Mississippi Valley Medical Editors' Association will resume annual meetings at the Jefferson Hotel, St. Louis, September 25, during the meeting of the Mississippi Valley Medical Society. This will be a dinner meeting, with three well known medical editors as speakers. A discussion period will follow each paper. All interested in medical writing are cordially invited to attend. A detailed program may be secured from the Secretary, Harold Swanberg, M.D., 209-224 W. C. U. Bldg., Quincy, Ill.

American Society for Research in Psychosomatic Problems, Inc.—The following officers were elected at the third annual meeting held at the Pennsylvania Hotel, New York city, May 11 and 12, 1946:

Adolf Meyer, M.D., Honorary President (continued)

Edward Weiss, M.D., President

Edwin G. Zabriskie, M.D., Secretary-Treasurer (continued)

Book Reviews

Constitutional Medicine and Endocrinology. By E. Pulay, M.D., A. P. Cawadiaz, M.D., and P. Lansel, M.D. Volume 1. Price, 10s. 6d. Pp. 99. London: Frederick Muller, Ltd., 1946.

This book, "Constitutional Medicine and Endocrinology," is stated to be the first of a series of monographs bearing this title. This volume is made up of a number of essays: "Constitutional Medicine, Metabolism and Endocrinology," "Addisonism or the Hypotonic Symptom Complex," "Pathophysiology of the Blood Picture," "Haemopoiesis and Constitution" and "Clinical Aspect of the Blood Sedimentation Rate."

The first essay by Cawadiaz is a thoughtful presentation, although unnecessarily verbose. The thesis is that constitutional medicine is a branch of internal medicine distinct from such subspecialties as cardiology and dermatology. It has to do with what are generally considered metabolic and endocrinologic disorders. It is concerned with the organism or patient as a whole. Its virtue would appear to consist of an emphasis on an approach to the chemical reactions of the body as a whole, and an integration of them. The remainder of the essays have very little to recommend them. They are replete with such pseudoscientific statements as, "Many cases of adrenal-cortex deficiency are to be expected from a lack of vitamin (fruit)" or ". . . many cases of asthmatic attacks are interrelated with hypoglycemia due to hepatic disorders caused by pituitary insufficiency."

The development of a broader concept in constitutional medicine is an attractive possibility. However, the essays in this volume chosen to illustrate this conception are very discouraging. This is a disappointing book.

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CORONARY ARTERIOSCLEROSIS, CORONARY ANASTOMOSES AND MYOCARDIAL INFARCTION

A Clinicopathologic Study Based on an Injection Method

A. RAVIN, M.D.

AND

E. F. GEEVER, M.D.

DENVER

IN 1938 Schlesinger¹ described a method for the postmortem study of changes in the coronary arteries which has opened a new field in the study of diseases of the coronary artery. At the University of Colorado School of Medicine 166 hearts have been studied thus far by the Schlesinger method. With this technic the right and left coronary arteries of the unembalmed heart are cannulated, and a mixture of agar and a lead salt is injected into the arteries. The agar is coagulated by cooling the heart, which is then unrolled by a series of incisions so that the coronary arteries are flattened out into one plane. The lead salt in the injection mixture is opaque to roentgen rays, and a roentgenogram is taken of the heart. An example of the roentgenogram which is obtained is shown in figure 1 I, in which the various parts of the heart are indicated. The mass which is injected into the right coronary artery is colored red with carbolfuchsin, and that in the left coronary artery is colored blue with methylene blue. After the roentgenogram has been taken the arteries are opened with fine scissors, and the color of the injected mass and the state of the arterial wall are indicated on a semi-transparent paper copy of the roentgenogram. This is easily determined; because the arteries are filled with the mass and the arterial walls are colored by the dye. A coarse reproduction of the roentgenogram in figure 1 I with the colors indicated is illustrated in the sketch, figure 1 II. Normally, no mixing of the mass injected into the two arteries occurs. This was proved in a number of hearts in which one or the other of the arteries was not injected because of faulty technic; the mass filled

From the Departments of Medicine and Pathology, University of Colorado School of Medicine.

Dr. J. J. Waring, Professor of Medicine at the University of Colorado School of Medicine, made this study possible and gave many valuable suggestions.

1. Schlesinger, M. J.: Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *Am. Heart J.* 15:528 (May) 1938.

only the artery injected. It did not extend in retrograde fashion into the other vessel:

The injected mass always penetrates to arterioles 40 microns in diameter and reaches about 50 per cent of the vessels 20 microns in diameter.¹ The normal failure of the colors to mix indicates that, in the normal heart at least, there are no anastomotic vessels greater than 20 to 40 microns in diameter. If anastomotic vessels greater than 20 microns in diameter are present mixing of the masses and of their colors occurs. Where such mixing occurs the resultant mass is purple.

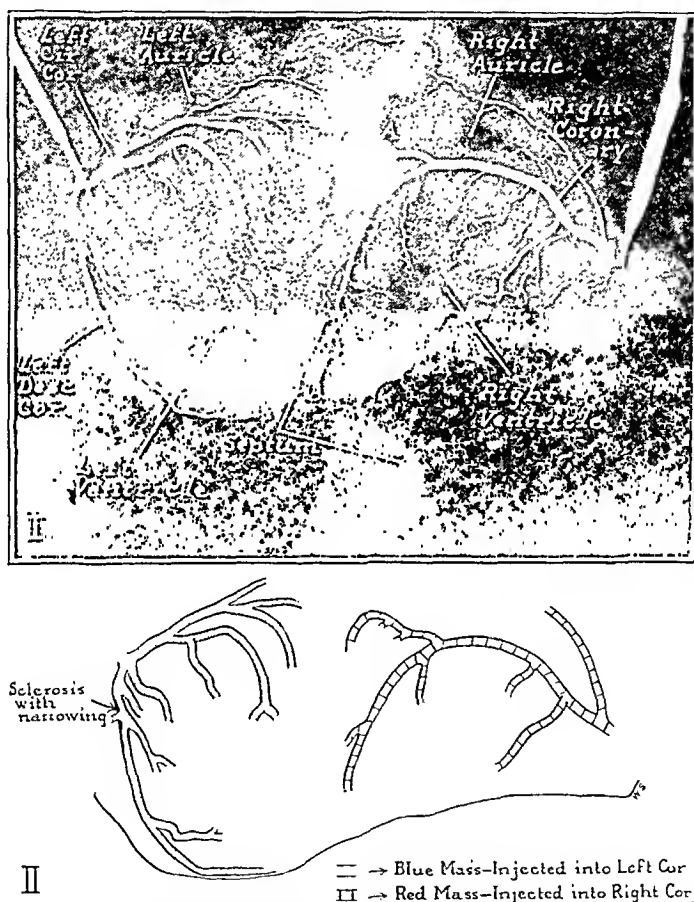


Fig. 1.—I, roentgenogram of the unrolled heart with the injected coronary arteries and anatomic landmarks labeled. *A* and *B* indicate the posterior cardiac wall at its junction with the interventricular septum. Small artefacts in the left circumflex artery are indicated at *C*. The arterial pattern is the balanced type. II, sketch reproducing grossly the main features of the roentgenogram in *I* and indicating the distribution of colors in a normal heart.

RESULTS

Except for less than a half-dozen hearts which were brought to us because they were expected to show changes, our series of 166 hearts was unselected and included a wide range of pathologic conditions. Thus in many cases the heart was normal, and the cause of death was unrelated to it. Eighteen hearts revealed coronary occlusions; of this

group 7 specimens showed more than one occlusion. In 14 hearts the occlusions were due to acute or subacute coronary thrombosis. Thirty-six hearts revealed interarterial anastomoses. The ages of the patients whose hearts were studied post mortem had varied from less than 1 year to 90 years, and the number of patients in each decade is listed in the accompanying table.

Results of Postmortem Study of Changes in Coronary Arteries

Age Group, Yr.	Number in Each Group	Coronary Pattern			Coronary Occlusions				Myocardial Infarction Without Occlusion	Anastomosis	
		Right	Balanced	Left	All Types	Multiple	Without Infarction	With Infarction		All Types	Without Occlusion
<10	2	2	0	0	0	0	0	0	0	0	0
11-20	5	1	4	0	0	0	0	0	0	1	1
21-30	15	7	5	3	0	0	0	0	0	0	0
31-40	8	4	3	1	1	1	1	0	0	1	0
41-50	23	13	7	3	3	2	1	2	0	6	3
51-60	42	20	17	5	6	1	2	4	1	11	6
61-70	33	19	10	4	3	2	1	2	0	7	5
71-80	27	13	11	3	3	1	0	3	1	8	6
81-90	11	7	2	2	2	0	0	2	0	2	0
Total	166	86	59	21	18	7	5	13	2	36	21

Arterial Patterns.—Examination of the pattern of the coronary arteries showed pronounced variation. However, three main types as described by Schlesinger² were found. Figure 1 *I* illustrates the balanced pattern of coronary circulation. In it the left coronary artery through its anterior descending and circumflex branches supplies the left ventricle and the anterior half of the interventricular septum. The right coronary artery supplies the right ventricle and provides the branch which goes down the posterior interventricular sulcus and supplies the posterior half of the septum. Figure 2 *I* shows a preponderance of the right coronary artery. The right coronary artery supplies the area described above and, in addition, a portion of the left ventricle. Preponderance of the left coronary artery is shown in figure 2 *II*. The left coronary artery furnishes the branch which goes down the posterior interventricular sulcus and supplies the posterior half of the septum. In our series we found the right preponderant pattern in 52 per cent of the cases, the balanced pattern in 35 per cent and the left preponderant pattern in 13 per cent. However, separation between types was not sharp, and various gradations were seen. On the basis of a study correlating coronary artery pattern with infarct formation and healing, Schlesinger² decided that hearts with preponderance of the left coronary artery suffer most from the effects of coronary arteriosclerosis, hearts with balanced blood supply suffer least and hearts with a preponderance

2. Schlesinger, M. J.: Relation of Anatomic Pattern to Pathologic Conditions of the Coronary Arteries, *Arch. Path.* 30:403 (July) 1940.

of the right coronary artery are intermediate in their response. The number of cases on which his conclusions were based seems inadequate. An analysis of the cases in this series does not support his conclusions, but in our series, again, there are too few cases. A much larger series will have to be analyzed before any decision can be reached.

Anastomoses Without Occlusion.—As has been said, mixing of the masses injected in the two arteries normally does not occur. This is



Fig. 2.—Roentgenograms illustrating the pattern of coronary artery preponderance. *I*, the right coronary artery supplies all the right ventricle, furnishes the descending artery on the posterior half of the interventricular septum and also supplies a portion of the left ventricle. *A* and *B*, the posterior cardiac wall at its junction with the interventricular septum. *C*, a small artefact. *II*, the left coronary artery supplies all of the left ventricle and furnishes the descending artery which supplies the posterior half of the interventricular septum.

true even in the hearts of persons of advanced age, if coronary sclerosis is minimal or moderate in degree. If, however, the coronary arteries become extremely sclerotic and narrowing of the lumen occurs, anastomoses may develop. Figure 3 *I* shows the sketch obtained of the injected heart of a 74 year old man who had severe bronchiectasis for fifteen years prior to his death. The onset of his disease had followed the aspiration of a chicken bone, and at autopsy a bone was found in one of the bronchi. Orthopnea had developed four weeks before his admission to the hospital, and severe dyspnea two days before his admission. He had bronchopneumonia and died shortly after entering the hospital. The heart weighed 320 Gm. and was grossly not remarkable. Owing to arteriosclerotic changes, the branches of the left coronary artery near their origin were decidedly narrowed. When these branches were opened it was found that the mass was colored not blue but purple—indicating that there had been an admixture of the red and blue masses. Anastomotic channels had formed, so that the mass (and blood) went from the right coronary artery into the left.

In figure 3 *II* the formation of anastomoses is even more definite. This is the heart of a 62 year old man who had silicosis and chronic nephritis and died of bronchopneumonia. The heart was enlarged (556 Gm.) and showed some hypertrophy of both ventricles. Microscopically there was some diffuse fibrosis. No occlusions were present, but under the stimulus of a narrowing of the arterial lumen due to arteriosclerosis, anastomoses had formed which helped to supply the left ventricle with blood. Anastomoses without occlusions were found in 21 hearts.

Occlusion Without Infarction.—It is comparatively easy, then, to proceed to the next step, the heart in which a coronary artery becomes entirely occluded without the occurrence of myocardial infarction. Figure 4 shows the roentgenogram and the sketch of the heart of a 67 year old woman who had had severe and long-standing myxedema, untreated at the time of death. She was admitted to the hospital with a fracture of the pelvis. Her heart was enlarged and she had hypertension. She died suddenly five days after admission. The heart weighed 460 Gm. and showed many interesting features, including aneurysmal dilatations of the coronary arteries—well shown in figure 4 *I*. Complete occlusion of the anterior descending coronary artery was caused by an old thrombus. The circulation beyond this was maintained by the left circumflex and right coronary arteries. No gross evidence of infarction was found; microscopically there was some scattered fibrosis but nothing which could be recognized as an infarct.

Figure 5 shows the roentgenogram and the sketch of the heart of a 39 year old man who had pulmonary and genital tuberculosis and at the time of his death had a pneumothorax on the right side. There was

nothing in his history to suggest cardiac disease, unless his complaint of epigastric pain after eating for several months prior to his death is so considered. At 10 o'clock one morning he experienced severe substernal pain requiring large doses of morphine for relief. Six hours later severe tachycardia and arrhythmia of complicated origin developed, and he died sixteen hours after the onset of the acute condition. The right coronary artery showed a complete old occlusion. Circulation was maintained beyond the point of occlusion by anastomoses between the left circumflex artery and the continuation of the right coronary artery. The blood in the continuation of the right coronary artery was actually flowing in a

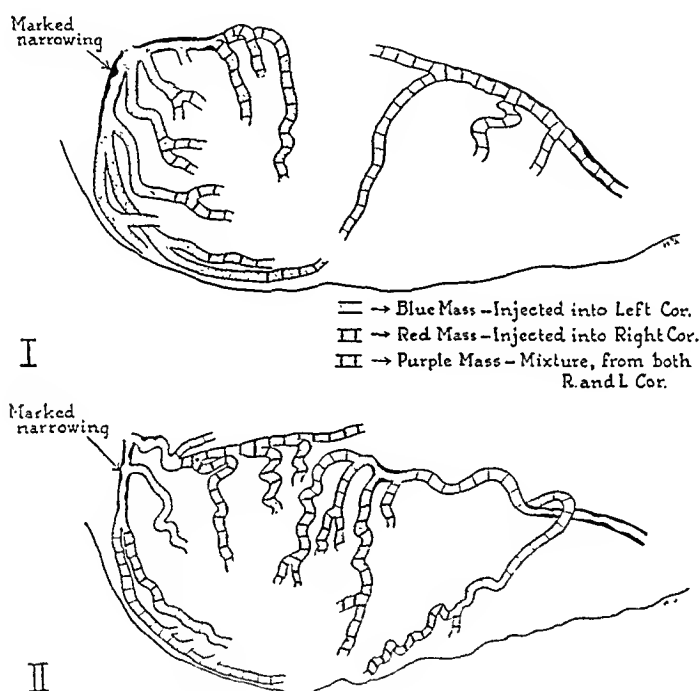


Fig. 3.—Sketches indicating distribution of colors as a result of anastomoses. *I*, anastomoses from the right coronary artery to the left in a 74 year old man with coronary arteriosclerosis but without occlusion. *II*, anastomoses in a 62 year old man with coronary arteriosclerosis but without occlusion. Anastomoses more devious than in *I*.

retrograde direction. No infarction was present, and nothing in the history indicated when the occlusion had occurred. In the left anterior descending artery there was a fresh thrombus with complete occlusion—this had undoubtedly accounted for the acute episode starting sixteen hours before death. The artery beyond the occlusion was filled with a purplish mass indicating anastomoses between the anterior descending artery and the circumflex artery and the right coronary artery. Sixteen hours would have been time enough for an infarct to have formed, but because of the anastomoses there was no infarction; microscopically some inflammatory change was found, but no myocardial necrosis. We

had 5 cases of occlusion without infarction in our series. However, there were 5 additional cases in which infarction occurred only after multiple occlusions.

Occlusion With Infarction.—It is evident from the foregoing statements that one of the main coronary arteries may become occluded without infarct formation if the occlusion occurs slowly enough and anastomoses have time to form. On the other hand, if the occlusion occurs

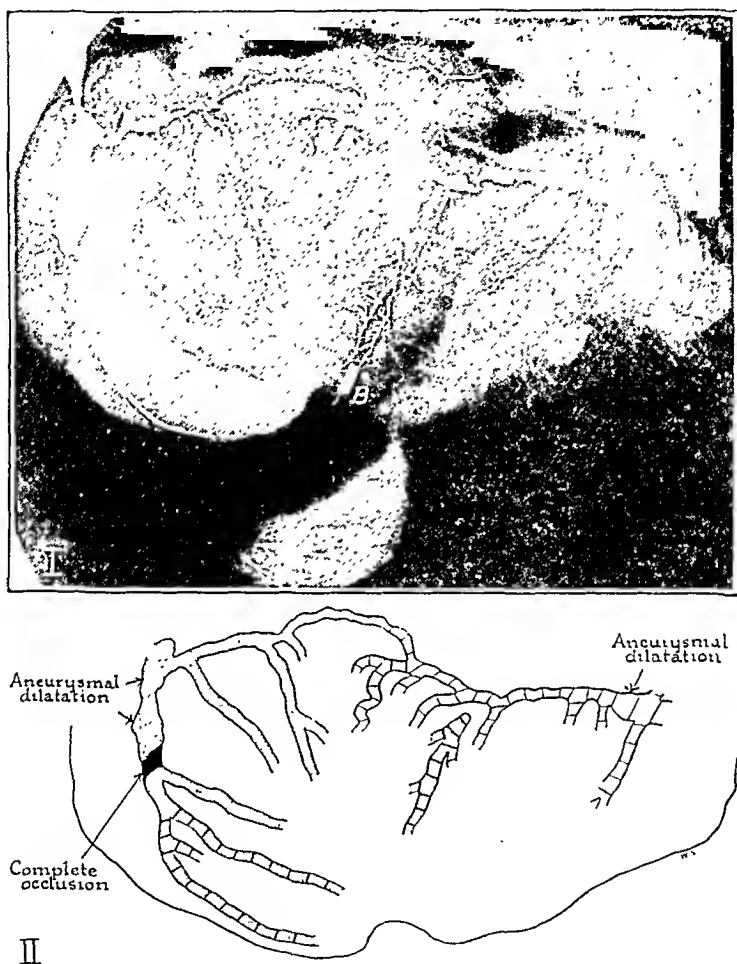


Fig. 4.—*I*, roentgenogram illustrating aneurysmal dilatations of the left anterior descending coronary artery with complete occlusion by an old thrombus at *C*. No gross myocardial infarct was present. The right coronary artery also shows aneurysmal dilatations. Breaks in the continuity of other arteries are artefacts. *A* and *B*, the posterior cardiac wall at its junction with the interventricular septum. *II*, sketch reproducing grossly the main features of the roentgenogram in *I* and indicating the distribution of colors (as in fig. 3) as a result of anastomoses. The left anterior descending artery beyond the occlusion is supplied by the left circumflex and right coronary arteries.

rapidly or, for some other unknown reason, anastomoses do not form coronary thrombosis is followed by myocardial infarction. Figure 6 shows a sketch of the injected heart of a 74 year old woman who had an acute cardiac episode a week before her sudden death. Anastomoses

were minimal, and infarction followed coronary thrombosis. There were 13 cases of occlusion with infarction in our series.

Infarction Without Occlusion.—It is well to emphasize here what must already be clear: Coronary thrombosis and myocardial infarction are not synonymous terms. This has been pointed out by Blumgart, Schlesinger and Zoll.³ It is substantiated in figure 7, which illustrates the injected heart of a 79 year old man who entered the hospital with the

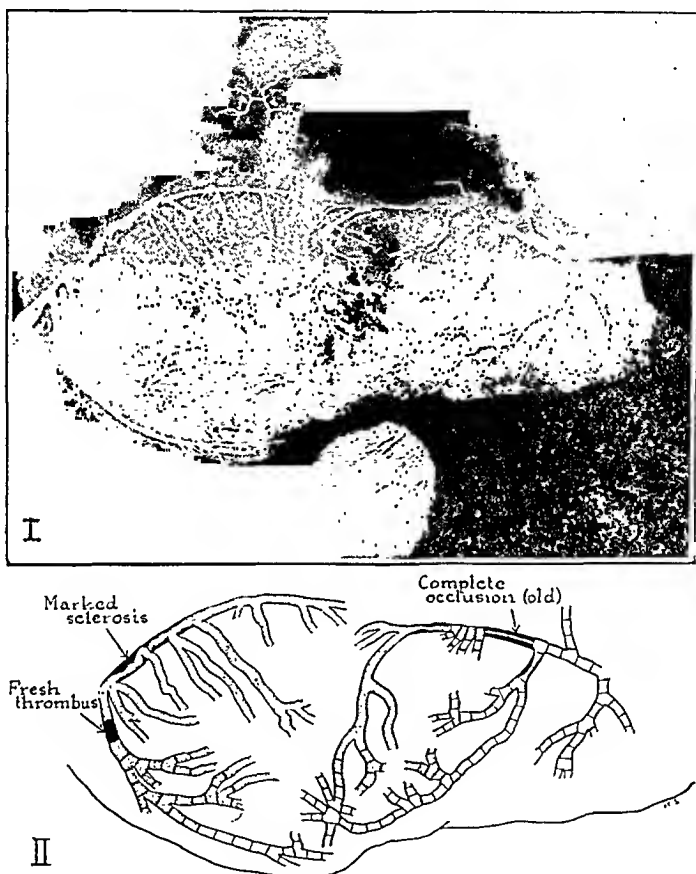


Fig. 5.—I, roentgenogram illustrating a complete old occlusion of the right coronary artery at C with a barely discernible recanalizing vessel. Fresh thrombus in the left anterior descending coronary artery at D. Note the numerous clearly visible anastomoses. II, sketch reproducing grossly the main features of the roentgenogram in I and indicating the distribution of colors (as in fig. 3) as a result of anastomoses.

diagnosis of senility, malnutrition and dermatitis and who died of bronchopneumonia. This heart showed no coronary occlusions and yet contained a myocardial infarct of moderate size, grossly evident and confirmed microscopically. The number of such cases reported in

3. Blumgart, H. L.; Schlesinger, M. J., and Zoll, P. M.: Angina Pectoris, Coronary Failure, and Myocardial Infarction, J. A. M. A. **116**:91 (Jan. 11) 1941.

the literature⁴ is increasing. The explanation would seem to be as follows: A myocardial infarct will form if an area of muscle becomes anoxic for a sufficiently long time. This may occur as a result of diminished blood supply following coronary thrombosis if sufficient anastomoses have not formed (figure 6). Anoxemia may also occur if the oxygen demand of the heart is increased by physical exertion, tachycardia or some other reason and the blood supply cannot be

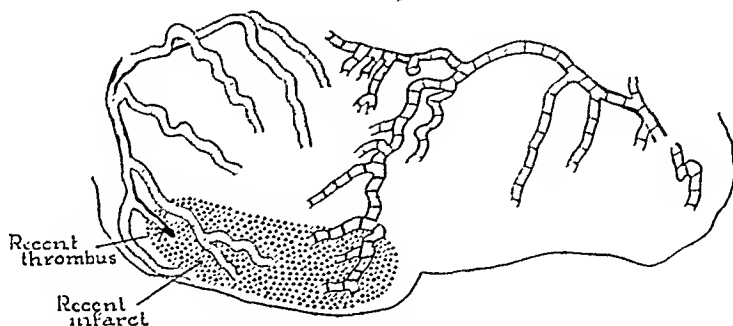


Fig. 6.—Sketch indicating a recent thrombus in the left anterior descending coronary artery with secondary infarction. Distribution of colors (as in fig. 3) and inadequate anastomoses shown.



Fig. 7.—Roentgenogram of a heart with an infarct of moderate size indicated by crosshatching. No coronary arterial occlusion present, but there is moderate to decided sclerosis in the main stems. *A* and *B*, the posterior cardiac wall at its junction with the interventricular septum.

4. (a) Gross, H., and Sternberg, W. H.: Myocardial Infarction Without Significant Lesions of the Coronary Arteries, *Arch. Int. Med.* **64**:249 (Aug.) 1939. (b) Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, *J. A. M. A.* **112**:1675 (April 29) 1939. (c) Holyoke, J. B.: Coronary Arteriosclerosis and Myocardial Infarction as Studied by an Injection Technic, *Arch. Path.* **39**:268 (April) 1945.

correspondingly increased because of extreme coronary narrowing due to arteriosclerosis. Anoxemia may result from a decrease in blood supply associated with anemia, shock, toxemia or tachycardia in a heart already handicapped by coronary arteriosclerosis. Experimentally, temporary coronary arterial occlusion for forty minutes will produce an infarct in the dog.⁵ It is reasonable to believe that more prolonged, if milder, anoxemia also can result in infarction. In our series we had 2 cases of infarction without coronary occlusion.

Hypoplasia of the Coronary Artery.—In a comparative examination of the injected hearts in our series we observed occasional striking variations in the caliber of normal vessels. Some hearts showed uniformly hypoplastic arterial systems. Such an example is presented



Fig. 8.—Roentgenogram of heart with uniformly small coronary arteries. Compare with arteries in figure 2I or 2II. A and B, the posterior cardiac wall at its junction with the interventricular septum. Fresh thrombus present at C and old occlusion at D. Note the numerous clearly visible anastomoses.

in figure 8, the roentgenogram of the heart of a 45 year old man. Note the difference in caliber of the coronary arterial system as compared with that shown in figure 2I—a somewhat smaller heart in a person of approximately the same age. The dangerous sequelae of arteriosclerosis, i. e. occlusions with or without thrombosis, are more likely to occur in a heart with congenitally small vessels than in one with arteries of normal caliber. This was borne out in the case illustrated by figure 8,

5. Blumgart, H. L.; Gilligan, D. R., and Schlesinger, M. J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries: II. The Production of Myocardial Infarction, *Am. Heart J.* 22:374 (Sept.) 1941.

in which fatal infarction occurred. We intend to present a future report on the results of more extensive studies of hypoplasia of the coronary artery.

Coronary Arteries in Patients of Advanced Age.—The hearts of the 11 patients over 80 years of age are worthy of brief comment. Only 2 specimens of this group showed significant coronary pathologic changes: arteriosclerosis, thrombosis, infarction and anastomoses. In the remaining 9 hearts we found mild to moderate arteriosclerosis and scattered myocardial fibrosis, usually detectable only on microscopic examination.

Anomalies of the Coronary Arteries.—Of the three main stems, the left circumflex artery showed the most frequent variation. In several hearts the size and distribution of this vessel were remarkably decreased. In 1 case the left circumflex artery was absent and the area normally supplied by it was nourished by the right coronary artery. One heart had complete absence of the right coronary artery. The left circumflex branch was a long vessel which took over the function of supplying the right ventricle. It also supplied a descending branch along the posterior border of the intraventricular septum. Death in this patient was of extracardiac origin, and adequate coronary circulation could be assumed despite the anomaly.

COMMENT

The clinical implications of the facts presented warrant consideration, particularly with reference to the prognosis and therapeutics of coronary arterial disease. Each heart as its vessels become sclerotic shows a balance between the rate of narrowing of the coronary artery and the development of anastomoses. In spite of much research, it is not known what factors, other than possibly age, anoxemia, fat metabolism and mechanical wear, are involved in the rate with which arteriosclerosis occurs. It is known that the narrowing of a vessel predisposes to formation of anastomoses. Why the narrowing should predispose to anastomoses and what other factors influence their formation have not yet been determined. Some day control of the factors favoring arteriosclerosis and those favoring the formation of anastomoses may open a new field in cardiac therapeutics.

The balance between the rate of development of arteriosclerosis and the rate of formation of anastomoses will decide what will happen. If the narrowing occurs rapidly and the formation of anastomoses is slow, then thrombosis, or occlusion from any other cause, will produce an area of decidedly anoxemic cardiac muscle with a resultant infarct. The classic clinical picture of myocardial infarction then occurs: initially, severe pain, shock and collapse; later, evidence of myocardial weakness and of inflammation, such as fever, leukocytosis and elevated sedimentation rate. The electrocardiographic changes are usually diagnostic.

If the narrowing of the vessel occurs slowly and adequate anastomoses form, it is possible for thrombosis to occur with little or no evidence of myocardial involvement. The collateral circulation is so adequate that only minimal change occurs in the muscle. This may consist of a mild inflammatory reaction due to anoxemia or inflammation and microscopic focal areas of necrosis. Clinically the patient may have an attack of mild or moderately severe substernal pain which passes off in a few minutes or an hour, and he may feel somewhat "under the weather" for a few days. The entire episode may be passed off as an attack of indigestion or neuritis and may soon be forgotten. The electrocardiogram may show no changes in spite of careful and repeated search, or it may show clearly recognizable changes which last for only a few hours or days and then return to normal. The temperature, pulse rate, blood count and sedimentation rate may be slightly elevated for a short time or may remain normal. These are the cases of coronary occlusion without infarction or, at most, with microscopic focal necrosis. Death may occur during one of these attacks due to the development of cardiac standstill or an arrhythmia, i. e., ventricular tachycardia and fibrillation; but the prognosis in most cases is otherwise good.

Between these extremes, changes of intermediate character may occur. If a moderate number of anastomoses have formed, the anoxemia is of an intermediate degree and the area of necrosis is smaller than would be expected from the size of the vessel occluded. The clinical symptoms would, of course, depend on the size of the infarct.

Two important conclusions may be drawn from the foregoing statements: The first is that the longer an occlusion is delayed in a patient whose coronary arteries are becoming sclerotic, the more time anastomoses have to form and the better the chance for survival with minimal damage. In a patient, therefore, in whom one has a warning of the presence of sclerosis, say in the form of angina of effort, any measure which postpones the eventual occlusion would be of great benefit. Such measures might vary in individual cases, but a decrease in activity and administration of coronary vasodilators would certainly seem indicated. From a legal standpoint it is also true that anything which precipitates a coronary occlusion sooner than it might have occurred, has medicolegal significance, even though it may be argued that the coronary occlusion would have occurred anyway.

The second point is that rest following a coronary occlusion is certainly of the greatest importance. In any area of the heart affected by a coronary occlusion, the ultimate fate of the fibers will depend on the degree of anoxemia to which those fibers are subjected. This, in turn, depends on the balance between the blood supply and the

oxygen requirement. If the oxygen requirement can be held down by rest, many fibers which might have become necrotic if forced to contract more frequently and more forcibly may survive. As the blood supply of the heart adjusts itself, these fibers may later have a sufficiently good supply of blood to increase their activity without anoxemia. In borderline cases, whether or not an infarct forms may depend on the load which is put on the heart.

As diagnostic acumen and laboratory methods improve and coronary thrombosis is recognized more often, the pessimistic concept of the prognosis will be modified. When only the more serious and the fatal cases were diagnosed this pessimism was justified. These studies show, however, that the heart is capable of making a better adjustment to thrombosis than has heretofore been expected. The patient can justifiably be encouraged and often can be prevented from acquiring a cardiac neurosis. Many years of enjoyable and even productive existence may follow an episode of coronary thrombosis.

In a heart manifesting severe arteriosclerotic narrowing of the coronary arteries, the muscle fibers may receive an adequate blood supply only when the patient is at rest. An increase in cardiac activity cannot be compensated for by an increase in coronary blood flow. This inadequacy is likely to occur in a heart which has had occlusions of one or of two of the main branches even if only minor or negligible infarcts have formed because of especially well developed anastomoses. Such delicately balanced hearts with a latent coronary insufficiency will be thrown into an acute or chronic coronary insufficiency by any factor which either increases the work of the heart or decreases the coronary blood flow. The work of the heart may be increased by exertion, ventricular tachycardia, infection, hypertensive crises and other factors. Shock, anemia, severe hemorrhage, heart failure and anoxemia from high altitude or from pulmonary conditions decrease the coronary blood flow and the oxygen available to the heart muscle. An electrocardiogram may show no changes when the patient is at rest but will show abnormalities when the muscle fibers become anoxic. The electrocardiographic changes produced in these hearts by low oxygen tensions⁶ and exercise⁷ have been used for diagnostic purposes. Repeated spells of acute coronary insufficiency produced by exertion may cause a sufficient degree of anoxemia in some fibers to result in necrosis, and over a long period many focal areas of necrosis may

6. Levy, R. L.; Patterson, J. E.; Clark, T. W., and Bruenn, H. G.: The "Anoxemia Test" as an Index of the Coronary Reserve, *J. A. M. A.* **117**:2113 (Dec. 20) 1941.

7. Master, A. M.; Friedman, R., and Dack, S.: The Electrocardiogram After Standard Exercise as a Functional Test of the Heart, *Am. Heart J.* **24**:777 (Dec.) 1942.

develop. This is commonly seen in patients with histories of angina pectoris. A severe degree of coronary insufficiency, even if temporary, may produce an area of infarction such as was found in the heart shown in figure 7.

In hearts with a latent or chronic coronary insufficiency another interesting phenomenon may occur—"infarction at a distance." A heart may have had a thrombosis of the left anterior descending artery and sufficient anastomoses may have formed to prevent the formation of an infarct. The right coronary and the left circumflex branch can take over the area formerly supplied by the anterior descending artery. Months or years later thrombosis may occur in the right coronary artery. The area most affected by this closure may be the area in the left ventricle which was previously supplied by the left anterior descending artery, and it is here that the infarct may form.

SUMMARY AND CONCLUSIONS

This is a presentation of the important observations in a series of 166 hearts in which the coronary arteries were injected and studied post mortem by the Schlesinger method.

The coronary arteries were occluded in 18 hearts. Seven specimens revealed more than one occluded vessel. Thirty-six hearts showed interarterial anastomoses. Anastomoses without occlusion were observed in 21 hearts.

Occlusion with infarction occurred in 13 hearts. Occlusion without infarction was encountered in 5 hearts. Infarction without occlusion of the coronary arteries was found in 2 hearts.

Some hearts showed uniformly hypoplastic arterial systems. In 1 case the hypoplasia was considered a factor in the death of a patient with arteriosclerosis, thrombosis and subsequent myocardial infarction.

In 11 patients over 80 years of age, 9 hearts showed mild to moderate arteriosclerosis and scattered myocardial fibrosis. The other 2 revealed advanced arteriosclerosis, anastomoses, occlusion and infarction.

Anomalies of the coronary arteries involved mainly the left circumflex vessel. In 1 case the right coronary artery was absent.

There is an important relation between the development of anastomoses and the prognosis and treatment of coronary arteriosclerosis and occlusion.

FULMINATING MENINGOCOCCIC SEPTICEMIA ASSOCIATED WITH ADRENAL LESIONS

An Analysis and Discussion of Seven Cases

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FOR HALF a century reports have been appearing in the literature describing a febrile illness which was characterized by the sudden development of a state of shock, by the prominence of hemorrhagic cutaneous rashes, by the remarkably early fatal termination and by the finding of adrenal hemorrhages post mortem. Exceptionally cutaneous eruptions were lacking, and occasionally the adrenal glands were not hemorrhagic.

Voelcker,¹ in 1894, was the first to describe this syndrome, followed by Waterhouse² in 1911 and Friderichsen³ in 1918. In time, the term "Waterhouse-Friderichsen syndrome" came to be applied to any illness of this nature, and this term has now become firmly entrenched in the literature. In none of the cases reported by those authors was the cause of the disease discovered, but in 1916 Maclagan and Cooke⁴ reported the occurrence of the syndrome in association with meningococcic meningitis.

There have been reported to date approximately 200 cases of the "Waterhouse-Friderichsen syndrome," with between fifteen and twenty recoveries. Prior to 1939 comparatively few of the reported cases were of proved meningococcic infections. Since then more and more have appeared, especially since 1943. The described pattern of the disease is fairly uniform, but laboratory data have been reported only infrequently and are somewhat conflicting. Postmortem studies in the main have been directed almost exclusively to the adrenal glands.

From the Medical Service, Regional Station Hospital, Fort Bragg, N. C.

1. Voelcker, A. F.: Pathologic Report, abstracted, Middlesex Hosp. Rep., 1894, p. 279.

2. Waterhouse, R.: A Case of Suprarenal Apoplexy, *Lancet* 1:577-579, 1911.

3. Friderichsen, D.: Nebennierenapoplexie bei kleinen Kindern, *Jahrb. f. Kinderh.* 87:109-125, 1918.

4. Maclagan, P. W., and Cooke, W. E.: Fulminating Type of Cerebrospinal Fever: Pathology and Causes of Death, *Lancet* 2:1054-1055, 1916.

It seems worth while to present 7 case histories in an effort to correlate the clinical, laboratory and pathologic factors involved. All 7 patients had fulminating meningococcic septicemia.

CLINICAL DATA

From January 1942 to January 1945, 214 patients with recognized meningococcic infections were admitted to this hospital. Of these, 131 had meningitis and 83 had meningococcemia only. The 7 cases of fulminating infection presented in this report represent 3.3 per cent of the total, an incidence rate which agrees exactly with figures cited in other sources.⁵ Two of the cases occurred in January, 2 in March and 1 each in April, August and December. Six of the patients were adult

TABLE 1.—*The Clinical Picture of Fulminating Meningococcic Septicemia*

	Case						
	1	2	3*	4	5	6	7†
Initial symptoms:							
Headache.....	+	+	..	+	+	+	..
Obill.....	..	+	..	+	+	+	..
Vomiting.....	+	+	+	+	..
"Head cold".....	+	+	+	+
Admission temperature, F....	103.8	104.6	106.4	..	98.0	99.2	..
Time from onset of illness							
To admission (hr.).....	1½	2	..	6½	4½	35	72
To onset of rash (hr.).....	3	±15	..	18	<4½	53	24
To onset of shock (hr.)....	12	24	..	18	<12	61	..
To onset of coma (hr.)....	13½	24	7	61	..
To death (hr.).....	37	20	..	†	59	†	72
Distribution of rash..... (in order of appearance)	Abdomen, chest, back extremities	Entire body	..	"Wide- spread"	Chest, abdomen, extrem- ities	Chest	..
Stiffness of neck.....	..	+	+
Positive Kernig sign.....	+	+	..
Cyanosis.....	+	+	..	+	..	+	..

* Patient moribund on arrival—no history obtainable.

† Patient dead on arrival—fragmentary history only.

‡ Patient recovered.

males ranging in age from 19 to 26, and 1 was an 11 month old white male child. One adult was a Negro. Of the 7 patients, 5 died and 2 recovered. The 2 patients who recovered went through just as stormy an illness, up to the point where recovery began, as did the 5 who died. One of the patients, a baby, was dead on arrival at the hospital, and only a meager history was obtainable. Another was dying when admitted, and no history was available. In the other 5 cases, however, reasonably complete histories were obtained. Pertinent data are recorded in table 1.

CLINICAL PICTURE

The illness began from one and a half hours to thirty-five hours prior to admission. Characteristically it was ushered in by headache, chills,

5. Weinberg, L. D., and McGavack, T. H.: The Waterhouse-Friderichsen Syndrome, *New England J. Med.* **232**:95-101 (Jan. 25) 1945.

vomiting and symptoms of a common cold. The temperature on admission ranged from 98 to 106.4 F. Most of the patients were at first treated as having a simple infection of the respiratory tract. A rash developed in 1 patient within three hours after onset, but as a rule there was none at the time of admission; however, in all of the patients hemorrhagic cutaneous lesions developed later, usually within twenty-four hours after the onset, the rash generally appearing first on the chest and the abdomen. Coincident with the appearance of the rash the temperature rose sharply, and concomitantly or shortly thereafter signs of shock appeared suddenly in the form of extreme weakness, pallor of the face, rapid thready pulse, falling blood pressure and cyanosis of the extremities; the interval of time between the onset of the illness and the change for the worse was usually from twelve to twenty-four hours. A semicomatose state ensued, followed rapidly by coma. Meanwhile the rash spread rapidly—so rapidly that in 1 case the “spots” could actually be seen “popping out” under the eyes of the attendants. From this point on, the patients who died went downhill rapidly, death occurring in from twenty-six hours to three days after the appearance of the first symptoms, while those who recovered gradually began to improve.

The rash will bear further description: Characteristically it consisted of purpuric or petechial lesions, but most of the patients also showed erythematous macules which frequently had petechial or purpuric centers; many of these lesions were tender to pressure. As the rash spread, it tended to become increasingly ecchymotic. One of the recovered patients exhibited a peculiar blotchy blush which appeared and disappeared almost rhythmically. The distribution of the eruption varied markedly; it usually appeared first on the chest and/or on the abdomen, the axillas and the shoulders, later involving the back, the arms and the lower extremities. The face was usually spared in the beginning. As the disease progressed, the lesions extended and coalesced, eventually involving sometimes as much as perhaps 80 per cent of the body surface. Involvement of the conjunctivas and of the oral mucosa was frequently seen, and in 1 case the uvula was black from extensive hemorrhage. In addition to the eruption, patchy areas of cyanosis frequently appeared, and over dependent parts a postmortem type of lividity was often present.

Most writers report that meningeal symptoms and signs are not common and that a lumbar puncture will usually reveal a normal cerebrospinal fluid. The present data do not bear this out. Of the 5 patients on whom a history could be obtained, all had headache as a major presenting symptom; 1 complained of soreness of the neck, and 2 had a positive Kernig sign—the one on admission and the other later in the illness. For 6 of the patients examinations of the spinal fluid were made (table 2), and for 3 of them they were repeated once.

Of the 3 who had only one puncture, 2 had a high cell count; of the other 3, who had two punctures, 2 had a normal cell count from the first specimen of fluid, but all 3 patients had counts showing a manifold increase from the second. It is worthy of note that it was from these same five fluids showing pleocytosis that meningococci were recovered (table 3). The probable reason for the prevailing misconception that the meninges are not involved is that stiffness of the neck

TABLE 2.—*White Cell Counts for Blood and Spinal Fluid*

Case	Blood				Spinal Fluid			
	White Cells		Neutrophils		White Cells		Neutrophils	
	Initial	Later	Initial, per Cent	Later, per Cent	Initial	Later	Initial, per Cent	Later, per Cent
1	7,900	71	..	2	100	..
2	11,950	27,200	86	87	2	2,200	100	97
3	10,750	32	..	500	100	..
4	8,850	33,100	92	97	2	2,240	50	46
5	8,000	26,650	72	84	5,150	98	..
6	18,150	81	..	35	9,000	94	94
7	Patient dead on arrival							

and the Kernig sign are usually absent; hence a spinal puncture is not done or else, when it is, it is done so early in the disease that the fluid is apt to be normal; in either case the possibility of meningitis is then dismissed from mind. To the possible criticism that the first puncture was responsible for the development of the meningitis, attention is called to the fact that in cases 2 and 4 the initial specimens, which each con-

TABLE 3.—*Results of Examinations of Blood and Spinal Fluid for Meningococci **

Case	Blood			Spinal Fluid		
	Smear	Culture	Group	Smear	Culture	Group
1.....	+	+	1	0	0	..
2.....	+	+	1	+	+	1
3.....	+	+	1	+	+	1
4.....	0	+	2 A	0	+	2 A
5.....	0	+	1	+	+	1
6.....	0	0	..	+	+	1
7.....	+	+	2 A	0	0	..

* The plus sign indicates that a meningococcus was recovered.

tained two cells, later yielded the meningococcus on culture, showing that even at this stage, before pleocytosis had occurred, the organism had already invaded the meninges.

Rapidly increasing leukocytosis was the rule, the highest count ranging from 18,000 to 33,000.

Blood cultures were positive for meningococci in 6 of the 7 cases (table 3). It is interesting that in 4 cases, all fatal, intracellular diplococci were found on routinely stained blood smears, a finding which

has been referred to in the literature as an "occasional" one. The spinal fluid revealed the meningococcus on either smear or culture or both in 5 of the 7 patients, and in the other 2 the blood culture was positive; hence in every case the cause was established beyond any reasonable doubt.

Of other laboratory findings, those to which attention has been called most frequently are albuminuria, increase in the nitrogenous elements of the blood and changes in the blood electrolytes. In the present cases, studies of the sodium and potassium ions were not made, but in some the nonprotein nitrogen, the creatinine, the chlorides, the sugar and the carbon dioxide-combining power of the blood were determined. The urinary findings are recorded in table 4 and the blood chemistry

TABLE 4.—*Urinary Findings*

Case	Albumin		Sugar	
	On Admission	At Peak of Illness	On Admission	At Peak of Illness
2.....	+	++	0	0
4.....	0	+++	++	0
5.....	++++	++++	Trace	0
6.....	0	+++	0	+++

TABLE 5.—*Chemical Studies of Blood and Spinal Fluid*

Case	Blood					Spinal Fluid Sugar, Mg. per 100 Cc.
	Nonprotein Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Chlorides, Mg. per 100 Cc.	CO ₂ -Combining Power	Sugar, Mg. per 100 Cc.	
1.....	75	1.7	478	..	126	..
			429			
2.....	86	3.2	396	63	130	75 52
3.....	20
4.....	39 28	...	462 531 445	43 58	114	93 48
5.....	75 92	2.9	479 479	..	147	54
6.....	45 32	0.7	418 413	49 64	266	67 62
7.....

levels and the sugar content of the spinal fluid in table 5. It is evident that the albuminuria and the azotemia reported by others were present in most instances; however, the 2 recovered patients (4 and 6) showed only slight azotemia although both had severe albuminuria. Glycosuria occurred in 3 patients and hyperglycemia in 4 (unrelated to the intravenous administration of dextrose). No other significant deviation from normal occurred, except the evidence of slight acidosis on the first examination in the 2 recovered patients.

Because the picture of shock is so striking in these patients, table 6 is included, showing the hematologic data pertinent to that condition in 3 cases. None of them showed the hemoconcentration characteristic

TABLE 6.—*Physical Properties of the Blood*

Case	Blood			Plasma	
	Hemo- globin, per Cent	Hema- tocrit, per Cent	Specific Gravity	Specific Gravity	Total Protein, Gm. per 100 Cc.
4.....	75	35	1.050	1.025	6.2.
	78	36	1.050	1.024	5.8
5.....	83	38	1.051	1.023	5.5
	85	39	1.052	1.023	
6.....	91	43	1.056	1.026	6.5
	92	41	1.058	1.030	7.9

of shock. This suggests that the shock exhibited by these patients is not that of blood concentration but is probably of a different nature.

TREATMENT

In 1 instance a sufficiently complete record of the treatment was not available, and in another the patient was dead on arrival. Of the 5 remaining patients 3 died and 2 recovered. These 5 were under treatment long enough to justify a report of the therapy employed,

TABLE 7.—*Summary of Therapy from Beginning of Treatment to Death or to Onset of Recovery*

	Case				
	2	3	4*	5	6*
Treatment period (hours).....	10	1	36	50	22
Penicillin (units).....	150,000	0	365,000	390,000	290,000
(units per hour).....	(15,000)	(0)	(10,000)	(3,800)	(13,200)
Sulfadiazine (Gm.).....	11	5	10	12	9
(Gm. per hour).....	(1.1)	(5)	(0.3)	(0.14)	(0.4)
Adrenal cortex extract (cc.).....	20	40	126	200	2
Desoxycorticosterone (mg.).....	0	0	10	15	0
Epinephrine hydrochloride aqueous solution, 1:1,000 (cc.).....	0	1	4.5	0.5	1
Epinephrine in oil, 1:500 (cc.).....	0	0	4	5	4
Plasma (cc.).....	0	0	500	250	500
Insulin (units).....	0	0	0	0	70

* Patient recovered.

although 1 was moribund on admission and died two hours later. Table 7 summarizes the treatment of these 5 patients from its institution until death occurred or until recovery began. A detailed account is appended to the paper.

In addition to the specific measures listed, all patients were given isotonic solution of sodium chloride intravenously in quantities which were thought to be sufficient and dextrose (except the patient in case 6).

REPORT OF CASES

CASE 1.—A 21 year old white soldier was admitted to the hospital at 5 p. m. on Aug. 17, 1943. He gave a history of headache, vomiting, coryza and generalized aching beginning about an hour and a half previously. His temperature on admission was 103.8 F. At 8 p. m. it was 105.2 F., by which time the patient was irrational and had a purpuric rash over the abdomen. A diagnosis of meningococcemia was made, and sulfadiazine therapy was begun. At midnight his temperature had reached 106 F. At 5 a. m., August 18, the patient was comatose. Purpuric lesions were then found on the chest, the back and the extremities, and the hands and the feet were cyanotic. The blood pressure was 96 systolic and 64 diastolic and the pulse 160 and respirations 60 per minute. On this day also (August 18) a direct blood smear showed diplococci phagocytosed by neutrophils, and a culture of blood was later reported positive for meningococci group 1. The rash spread; the patient lapsed into a deep coma; pronounced circulatory collapse followed, and the patient died at 4:40 a. m., August 19, approximately thirty-seven hours after onset.

No definite signs of meningitis had been observed. Unfortunately, the spinal fluid was not examined during life, but fluid obtained at autopsy showed slight xanthochromia and contained 2 cells per cubic millimeter; on culture no growth appeared after several days.

The autopsy was performed fifty minutes after death. A macular purpuric rash varying in color from purple to light red was present over the entire body; the borders of some of the macules were indurated. There were also numerous areas of ecchymosis varying from very large to petechial, and hemorrhages were likewise present in the conjunctivas. Beneath the hemorrhagic lesions of the skin there was usually a variable but moderate amount of blood extending into the subcutaneous tissue. Microscopic sections of the skin showed focal collections of blood cells extravasated into the dermis and subcutaneous fat.

A moderate number of small hemorrhages were present in the epicardium, especially around the base of the heart, and beneath the pleura, chiefly around the hilus. Submucous petechial hemorrhages were noted in the ileum and the lower part of the jejunum.

The liver appeared diffusely enlarged (weight, 2,170 Gm.). The capsule was thin, and its surface showed numerous small depressed stellate figures of a red color. The hepatic substance was found to be of a brownish yellow color and of a soft friable consistency. The stellate markings extended for a few millimeters into the substance. Microscopically, focal areas of necrosis and diffuse congestion of the central veins and surrounding sinusoids were evident. There was also a diffuse separation of the hepatic cords from the lining of the sinusoids.

The spleen was large (weight, 440 Gm.) and showed congestion of the pulp on microscopic examination.

Large submucous hemorrhages were found in the renal pelves. In addition, the microscopic examination revealed dilatation of the tubules with hyaline casts in their lumens.

Some hemorrhagic streaks were seen in the periadrenal fat. The adrenal glands were large but of normal contour. Both were heavily infiltrated with blood. The cortex measured 3 to 4 mm. in thickness. Microscopic examination revealed

massive extravasation of blood in the inner layer of the cortex and in the medulla (fig. 1). Hemorrhagic foci were also present in the outer layer (glomerular zone and external half of the fascicular zone). Areas of the cortex not involved by hemorrhage showed definite engorgement of the capillaries. These remnants of cortical tissue were composed of cells with a finely granular or homogeneous eosinophilic cytoplasm. In a few isolated instances, on the periphery of the gland, wherever the architectural details were not totally obscured by extravasated blood, conversion of the solid adrenal cords into "tubular" structures was observed. The lumens of the tubules contained cellular debris, polymorphonuclear leukocytes and,

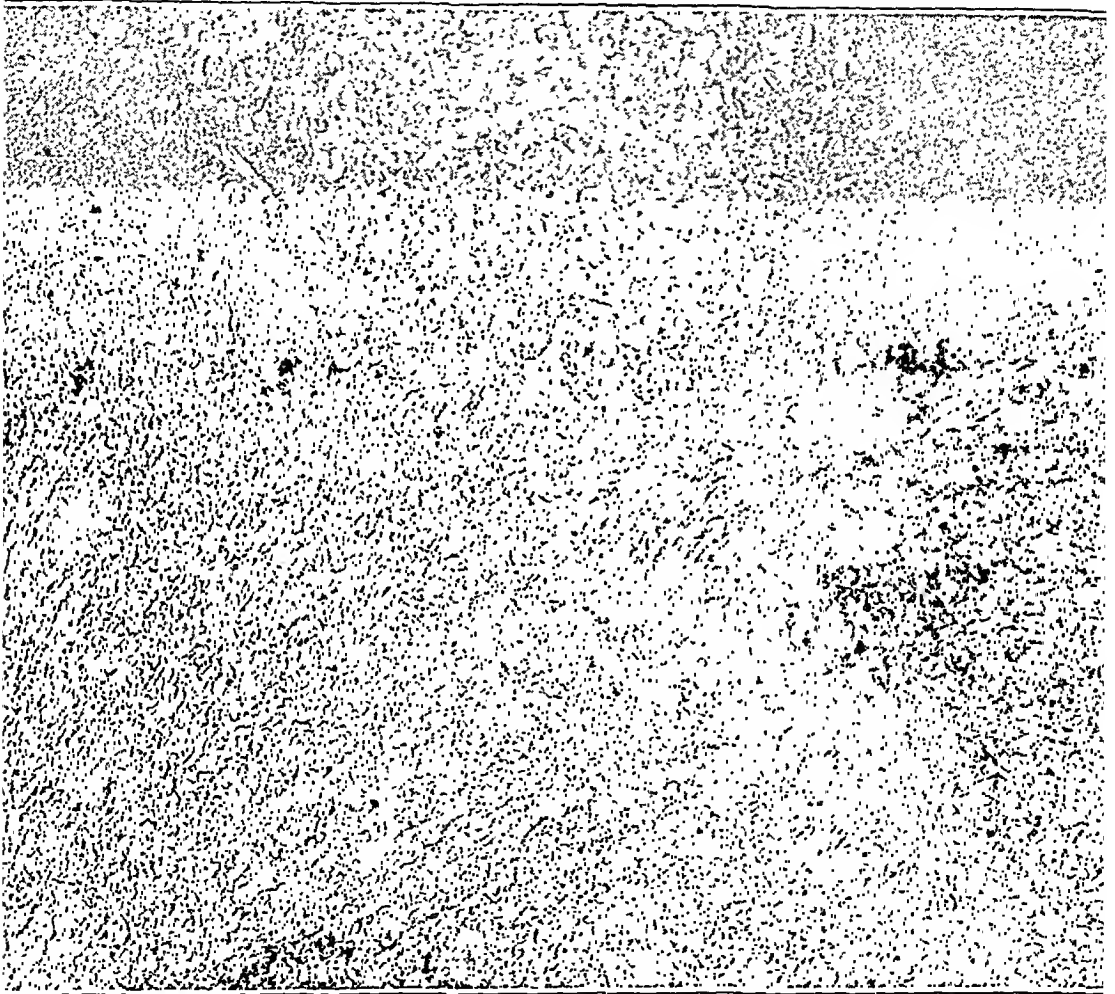


Fig. 1 (case 1).—Section of adrenal gland showing the most intense hemorrhagic changes localized in the reticular zone and the inner portion of the fascicular zones. $\times 50$. (United States Army Medical Museum negative 87500.)

in the zones immediately adjacent to the hemorrhagic areas, red blood cells. The cells lining the lumens had undergone degenerative changes, with fraying of the cytoplasm and pyknosis of the nucleus in evidence. These changes were apparently identical with those of the lesions described by Rich⁶ and coexisted with the

6. Rich, A. R.: A Peculiar Type of Adrenal Cortical Damage Associated with Acute Infections and Its Possible Relation to Circulatory Collapse, *Bull. Johns Hopkins Hosp.* 74:1-15 (Jan.) 1944.

hemorrhagic changes, although obscured to a great extent by them and by the shrinking away of the cords from the walls of the capillaries. The latter phenomenon resulted in the formation of two parallel lumens, one on each side of a solid cord composed of two rows of cells.

The brain and meninges showed no conspicuous gross lesions. Microscopically, in both there were slight edema and minimal infiltration with cells of inflammatory origin.

CASE 2.—A 29 year old white soldier was admitted to the hospital at 3:30 p. m. on Jan. 22, 1944, about two hours after a sudden onset of weakness, shaking chills, fever, headache, pain in the back and exhaustion. The temperature on admission was 104.6 F. and the leukocyte count 11,950, with 84 per cent neutrophils. Physical examination revealed nuchal rigidity of minimal degree, but Kernig's sign was absent. The pharynx was moderately injected. A roentgenogram revealed that the chest was normal. Meningococci of group 1 were later recovered from the spinal fluid by culture. Early the next morning (Jan. 23) an increasingly widespread, mottled purpuric and ecchymotic rash developed over the entire body, including the face and neck, about 80 per cent of the body surface eventually becoming involved. There were scattered hemorrhagic spots, most of which were large, being an inch (2.5 cm.) or more in diameter. These were present also in the conjunctivas and mouth, the uvula being completely black from hemorrhage. In spite of treatment the eruption continued to spread. The patient became restless and complained of chilliness and burning and soreness "in spots." The lips, the finger nails and the entire skin became cyanotic; the pulse rate was 110, and the blood pressure was 130 systolic and 100 diastolic. Nuchal rigidity had not increased, and Kernig's sign was still absent. The leukocyte count was 27,200 with 87 per cent neutrophils. The temperature was 105 F. At 1:10 p. m. (Jan. 23) the patient became comatose and cyanotic, with rapid respirations. The temperature climbed to 107.8 F. (rectal), and then the respirations dropped to 8 per minute. A direct smear of the blood showed diplococci phagocytosed by neutrophils. The culture of blood was later reported positive for meningococci, group 1. In spite of all therapy, however, the patient died at 3:10 p. m., January 23, twenty-six hours after the onset. A second spinal puncture was done at the time of the autopsy, and the fluid contained 2,200 cells.

The autopsy was performed two hours after death. About 80 per cent of the body surface was covered with a macular rash which overlapped the intense post-mortem lividity over the dependent parts of the body and which involved completely the upper and lower extremities, the head, the face, the neck and the buttocks. The macules were of a deep purple with some variation in intensity. They appeared to be darker in areas where the skin was thin. The purpuric spots coalesced to a point that only islands of skin an inch (2.5 cm.) or less in diameter appeared normal in color. On the chest and the abdomen were numerous purplish red spots of irregular contour, but fairly large areas of intact skin were still visible. Numerous small, slightly raised and indurated petechiae were scattered over the entire body and were visible through the macular rash. Petechial hemorrhages were present in both conjunctivas. Sections of the skin showed pronounced venous and capillary congestion in the corium and subcutaneous fat. There was slight perivascular infiltration with polymorphonuclear leukocytes and lymphocytes.

Examination of the viscera revealed focal hemorrhages in the pulmonary parenchyma and petechial hemorrhages in the parietal pleura and the parietal and the visceral pericardium. A patch of hemorrhagic infiltration was present under the endocardial lining of the interventricular septum on the left.

The liver weighed 2,700 Gm. There was some spotty variation in color over the capsule, probably of hyperemic rather than of hemorrhagic nature. Microscopic examination showed congestion of the central and interlobular veins. The hepatic cords in the center of the lobules were atrophic. A sprinkling of polymorphonuclear leukocytes was noticed in the sinusoids and in the spaces between the sinusoids and the hepatic cords.

The spleen (weight 230 Gm.) showed congestion of the pulp and a diffuse increase in the number of polymorphonuclear leukocytes.



Fig. 2 (case 2).—Section showing "tubular changes" prominent in the external layers of the adrenal cortex. The dark streaks are congested sinusoids. Disruption of the cords and edema of the stroma in the deepest layer are evident. $\times 50$. (United States Army Medical Museum negative 87506.)

The adrenal glands showed no gross hemorrhages. Microscopically (fig. 2), there was pronounced congestion of the sinusoids but no extravasation. The cells in the glomerular zone displayed a vacuolated cytoplasm and appeared of average size, while those in the inner part of the fascicular and reticular zones had shrunk, their cytoplasm being homogeneous and dark and sprinkled with brown pigment. In this case the "tubular" changes in the outer half of the fascicular layer were prominent (fig. 3). The lesion was identical in every respect with that

described and discussed by Rich.⁶ The cords in the outer third of the fascicular zone were converted into tubules lined by vacuolated cells, many of which had undergone degeneration with fraying of the cytoplasm and pyknotic changes of the nuclei. Small collections of polymorphonuclear leukocytes were seen in the vicinity of these lesions. In some instances the adrenal cells had disappeared entirely from the inner layer of the cortex (fig. 4), leaving only a reticular stroma between the congested capillaries. The medulla was not remarkable.

The meninges were not conspicuously involved on gross examination, except for questionable cloudiness of the arachnoid along the sulci. Microscopically, there

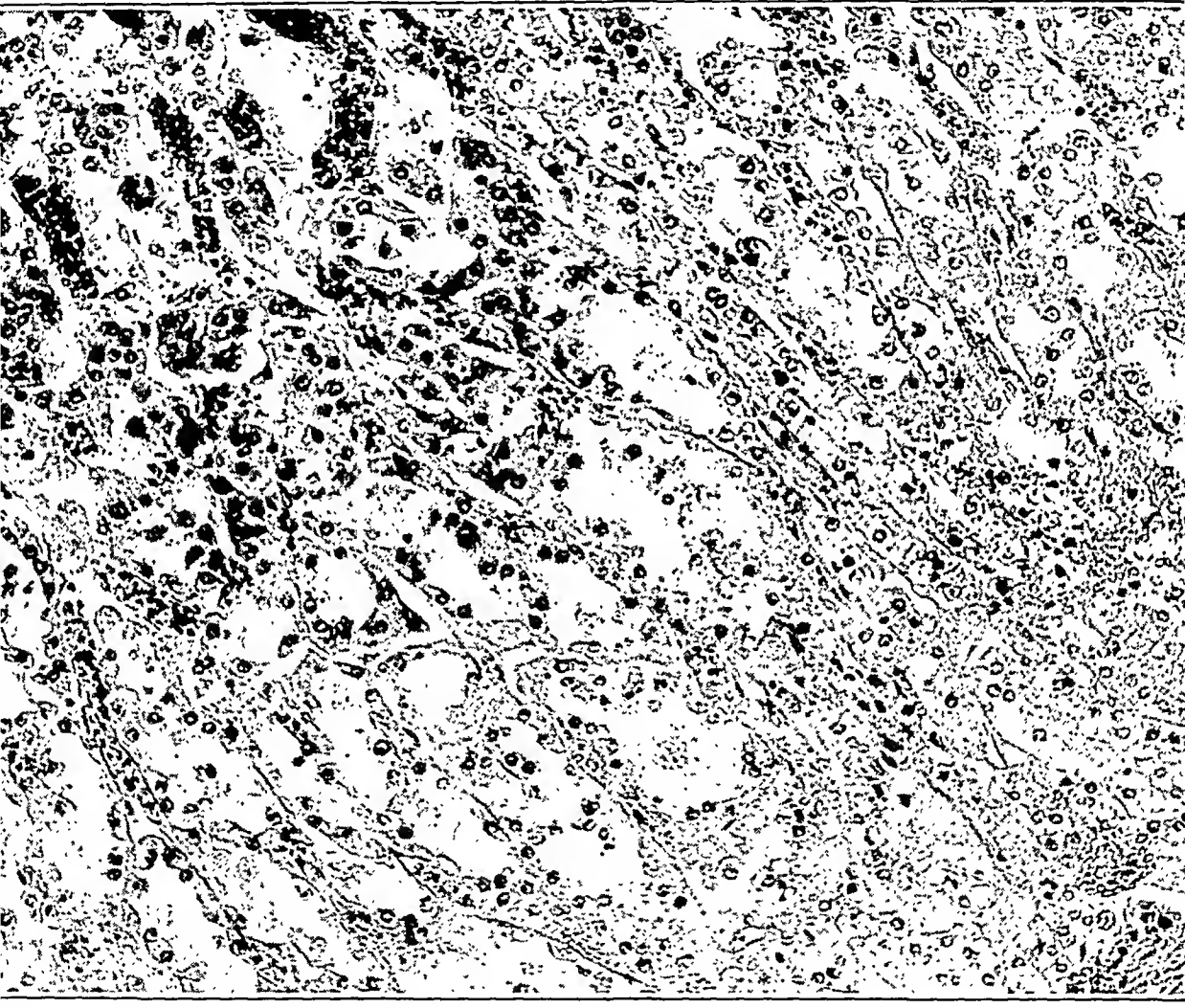


Fig. 3 (case 2).—Section of the superficial part of the adrenal cortex showing detail of the "tubular changes," and congested sinusoids. $\times 250$. (United States Army Medical Museum negative 87502.)

was a fair amount of acute inflammatory cellular exudate in the subarachnoid spaces.

CASE 3.—A 19 year old Negro soldier was admitted to the hospital at 11:45 a. m. on March 13, 1944, at the point of death with no available history. His skin was covered with a purpuric rash involving the chest, the face and the back, as well as the lips and the buccal mucosa. Hemorrhagic lesions were also noted

in the conjunctivas. There was no stiffness of the neck. The lungs were normal, and the heart sounds were faint. The temperature (rectal) was 106.4; the blood pressure was unobtainable and the pulse imperceptible. A diagnosis of fulminating meningococcic septicemia was made. The leukocyte count was 10,750, with 32 per cent neutrophils and 68 per cent lymphocytes. Diplococci phagocytosed by neutrophils were seen on direct blood smear, and culture of blood later yielded meningococci, group 1. The spinal fluid contained 500 cells and an abundance of meningococci. The patient died at 2 p. m. on the day of admission, the duration of his illness being unknown.

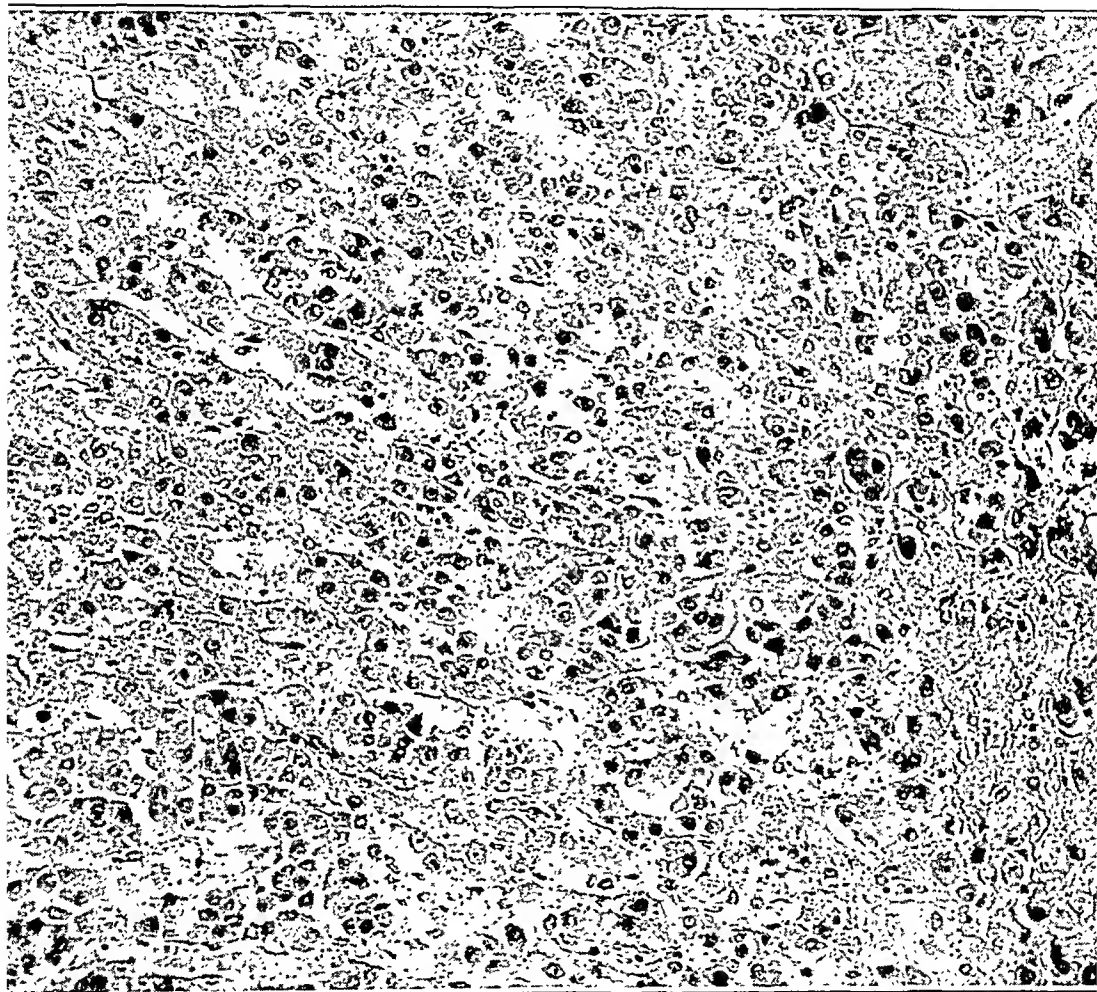


Fig 4 (case 2).—Section of the inner zone of the adrenal cortex showing in detail disruption of the cords, leaving isolated shrunken cells with homogeneous cytoplasm, and edema of the stroma. $\times 250$. (United States Army Medical Museum negative 87501.)

The autopsy was performed two hours after death. The skin was covered with numerous irregular blotchy purplish red spots over the face, the shoulders, the trunk, the abdomen and the extremities but not involving the hands and the feet. Small dark purple petechiae were seen over the forehead and the nasal ridge. Petechial hemorrhages were seen also under the palpebral and bulbar

conjunctivas. Sections through the macular cutaneous lesions revealed congestion of the venules and the capillaries, as well as some edema and cellular infiltration of the corium.

Examination of the viscera revealed petechial hemorrhages under the visceral pericardium of the heart and ascending aorta and under the serosa of the small intestine. There was also some hemorrhage beneath the endocardial lining of the left ventricle over the septum. In the course of the microscopic examination a few small focal hemorrhages were also found in the pulmonary parenchyma and in the thymic interstitia.

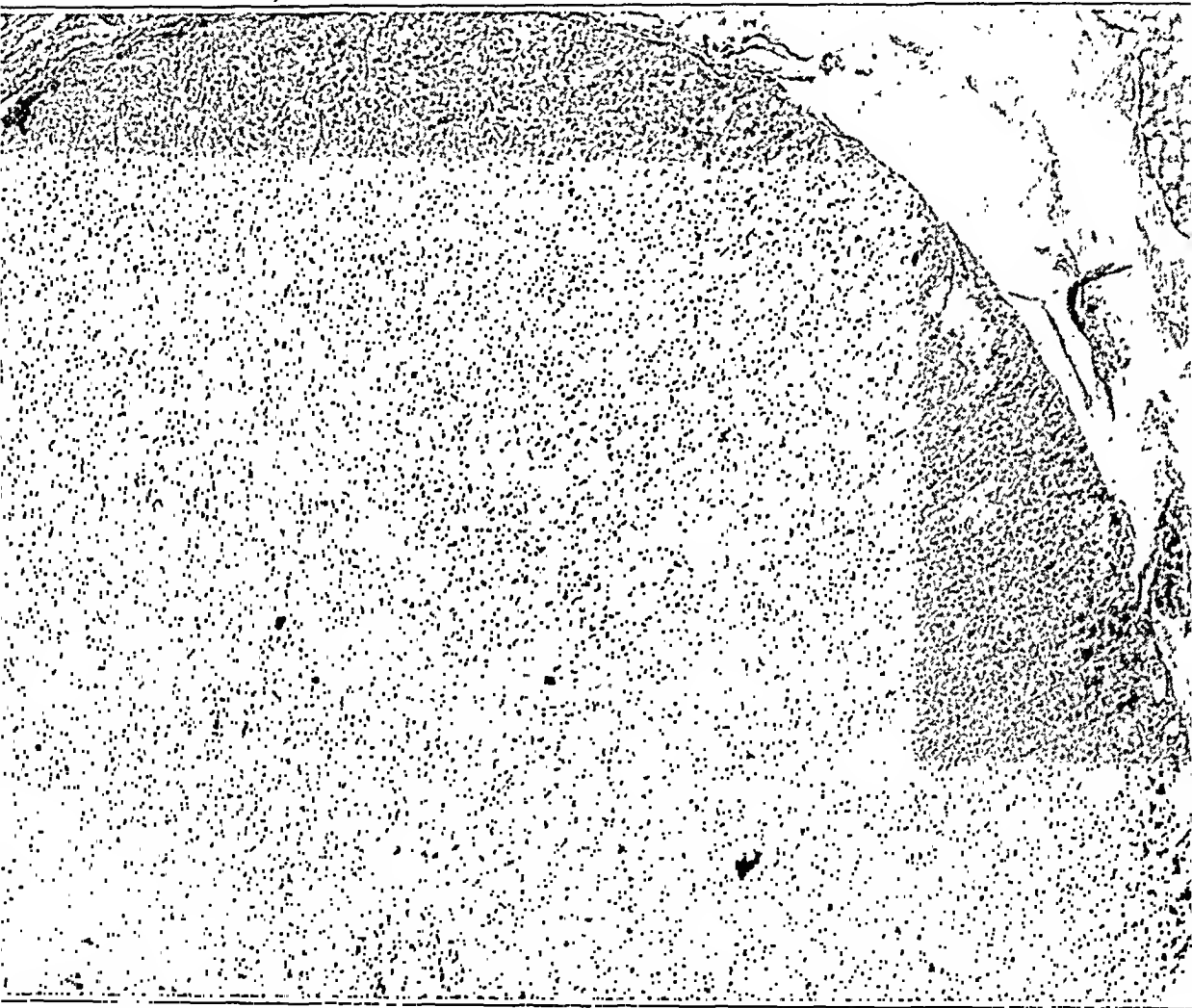


Fig. 5 (case 3).—Section of adrenal gland showing extensive hemorrhage of the inner portion and "tubular changes" in the outer. $\times 50$. (United States Army Medical Museum negative 87499.)

A reddish purple discoloration of both adrenal glands could be seen through the periadrenal fat and capsules. Their cut surfaces presented a diffuse hemorrhagic discoloration of the cortex and the medulla. Microscopic examination revealed diffuse hemorrhagic infiltration, most pronounced in the fascicular and reticular zones of the cortex (fig. 5). In the hemorrhagic zones the normal structure of the adrenal cords and cells was entirely obliterated by extravasated blood (fig. 6). A few islands of adrenal cortical tissue were preserved in the

outer glomerular zone of the cortex (fig. 7); and in these "tubular" changes were slight compared with those in case 1. A few extravasated blood cells were noted in the "tubular" lumens. The adrenal remnants were composed mostly of cells with solid or finely vacuolated cytoplasm. The medulla was not involved in the hemorrhage.

The brain surface showed an intensification of the vascular pattern and a diffuse hemorrhagic discoloration over both temporoparietal regions. Microscopically, a moderate amount of cellular inflammatory exudate was found in the

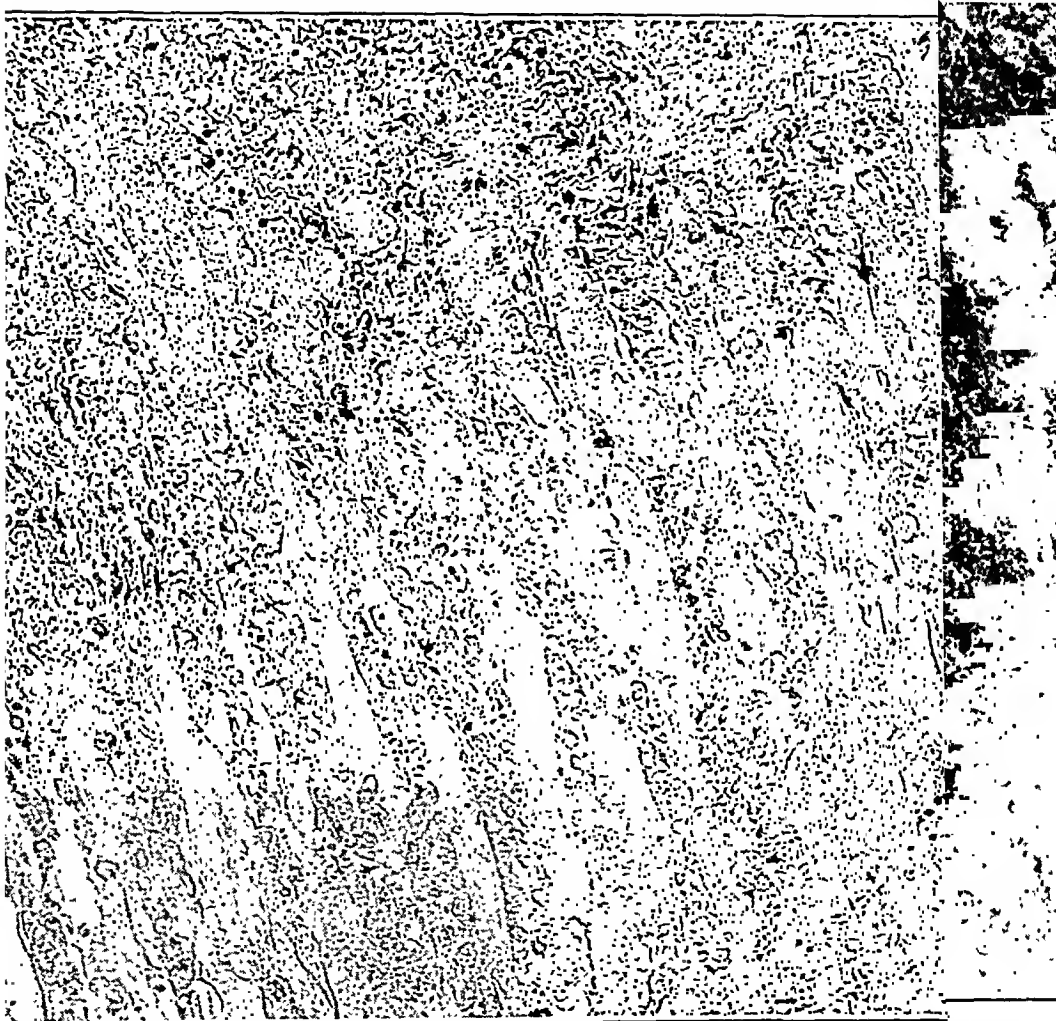


Fig. 6 (case 3).—Section of inner portion of adrenal gland showing hemorrhagic changes. $\times 250$. (United States Army Medical Museum 87496.)

subarachnoid space. A considerable number of red blood cells were mixed with the exudate.

CASE 4.—An 18 year old white soldier was readmitted to the hospital at 6:30 p. m. on March 28, 1944, having been hospitalized March 19 to 26 for a common cold. He gave a history of a sudden onset about noon of the day of admission, with headache, shaking chills, nausea, vomiting and pain and tightness in the lower portion of the left side of the chest. The leukocyte count was 8,050, with 67 per

cent neutrophils. Lobar pneumonia was suspected, but a physical examination and a roentgenogram revealed a normal chest. A lumbar puncture was done, the fluid being clear, with two cells; a culture of this fluid later yielded meningococci, group 2A. No therapy was instituted at this time. A later leukocyte count showed 24,300 cells, with 80 per cent neutrophils. On the following morning, March 29, pallor, cyanosis, weakness and a widespread and rapidly increasing purpuric rash rapidly developed; the pulse was imperceptible, and the blood pressure was unobtainable. The leukocyte count was 30,150, with 91 per cent neutrophils. Following therapy, slight improvement occurred, but by midafternoon the blood

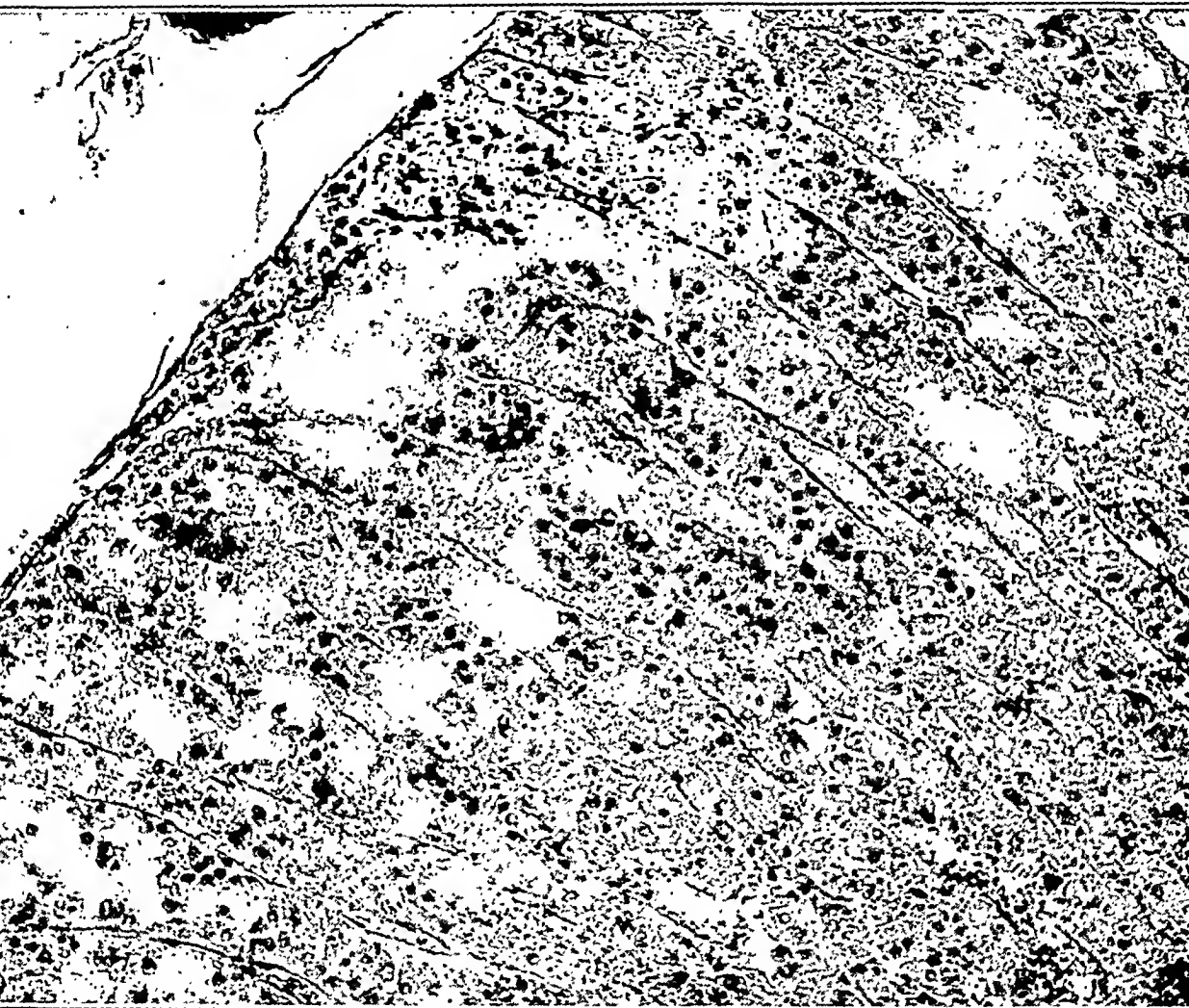


Fig. 7 (case 3).—Section of outer portion of adrenal gland showing detail of the "tubular changes." Red blood cells are seen in the tubular lumens. $\times 250$. (United States Army Medical Museum negative 87504.)

pressure had again fallen to an extremely low figure which could not be recorded, and severe pulmonary edema developed. The patient became moderately stuporous. Oxygen therapy and other measures were followed by some improvement. The condition of the patient remained precarious until 8 p. m. on March 30, when gradual but steady improvement began. He eventually made a complete recovery. Evaluation of adrenal function (sodium chloride restriction, water restriction and dextrose tolerance tests) a month later revealed normal conditions.

CASE 5.—A 26 year old white soldier was admitted to the hospital at 1:30 p. m. on April 13, 1944. He had had one previous admission, on Feb. 5, 1944, with a common cold, from which he made an uneventful recovery, being discharged five days later. Four and one-half hours before his present admission the patient had a severe shaking chill, headache and sore neck. He vomited once. His temperature on admission was 98 F., climbing one hour later to 104 F. The leukocyte count was 12,850, with 88 per cent neutrophils. Numerous petechiae were noted on the chest, abdomen and extremities, varying in size from that of a pinhead to about 3 mm. in diameter, and a few were also seen in the conjunctivas. The Kernig and Oppenheim reflexes were present. The blood pressure was 128 systolic and 72 diastolic.

The clinical course was progressively downhill. The patient became critically ill; marked nuchal rigidity developed and he became semicomatose about 4 p. m. The temperature rose to 105 F. A spinal puncture revealed cloudy fluid containing 5,150 cells per cubic millimeter, with 98 per cent neutrophils, and smears and culture were positive for meningococci, group 1. The same organisms were recovered from the blood and the nasopharynx. Sulfadiazine therapy was begun at 6 p. m., April 13. By 8:30 a. m. on April 14 the blood pressure and the pulse were imperceptible. At 6:30 p. m. the leukocyte count was 26,650, with 84 per cent neutrophils, and the blood pressure was 80 systolic and 60 diastolic. At 8:30 a. m. on April 15 the patient suddenly became much worse; the rash increased, and large purpuric lesions developed. The nonprotein nitrogen of the blood had increased from 75 mg. per hundred cubic centimeters on the fourteenth to 92 mg. on the fifteenth; the creatinine of the blood was 2.9 mg. per hundred cubic centimeters, and the blood sugar was 148 mg. per hundred cubic centimeters. Urinalysis showed albumin (4 plus) with 25 to 30 red blood cells per high power field, a few white blood cells and granular casts. In spite of all therapy the patient died at 8 p. m. on April 15, fifty-nine hours after onset.

The autopsy was performed thirteen hours after death. The cutaneous rash in this case showed a complete predominance of the petechial component over the purpuric. Numerous petechiae averaging 2 mm. in diameter were scattered over the chest, the abdomen, the arms, the thighs and the back. Only a few purpuric spots were seen; these were limited to the legs and the forearms and averaged about 2 cm. in diameter. Sections of the skin revealed edema of the corium and a slight diffuse lymphocytic infiltration with focal perivascular condensation. The sebaceous glands had undergone partial necrosis and were diffusely infiltrated with leukocytes. A few dilated arterioles below the corium were plugged with compact collections of fibrin, red blood cells and leukocytes; these were thought to be thrombi, responsible for the petechial lesions in the skin.

The pleural cavities each contained 300 cc. of clear fluid. The lungs were exceedingly wet, heavy and congested. There were patchy areas of increased consistency, presenting a mottled gray color on the cut surface, especially numerous in the posterior parts of the lungs. The sections showed edema, with fluid and fibrinopurulent exudate in the alveolar and bronchiolar lumens. The distribution of the exudate was patchy and its density variable.

The heart weighed 420 Gm. The myocardium was of a flabby consistency and a grayish tan; its cut surface revealed yellow and reddish purple mottling, and in some instances coalescent rounded yellow areas of discoloration were scattered throughout its superficial third, while the purplish red discoloration was most conspicuous midway between the pericardium and the endocardium. The papillary muscles in the left ventricle were involved in the changes, hemorrhagic spots being

present. Microscopic examination of the heart confirmed the gross evidence of acute myocarditis, revealing degeneration of the muscle fibers and polymorphonuclear and mononuclear leukocytes infiltrating the interstices. The degenerative changes in the fibers were far more pronounced than the cellular infiltration of the interstices.

The gastrointestinal tract was not remarkable except for esophageal erosions.

The liver weighed 2,180 Gm. The central veins and sinusoids were congested. The cell borders were indistinct, and the portal spaces were in some instances being infiltrated by leukocytes.

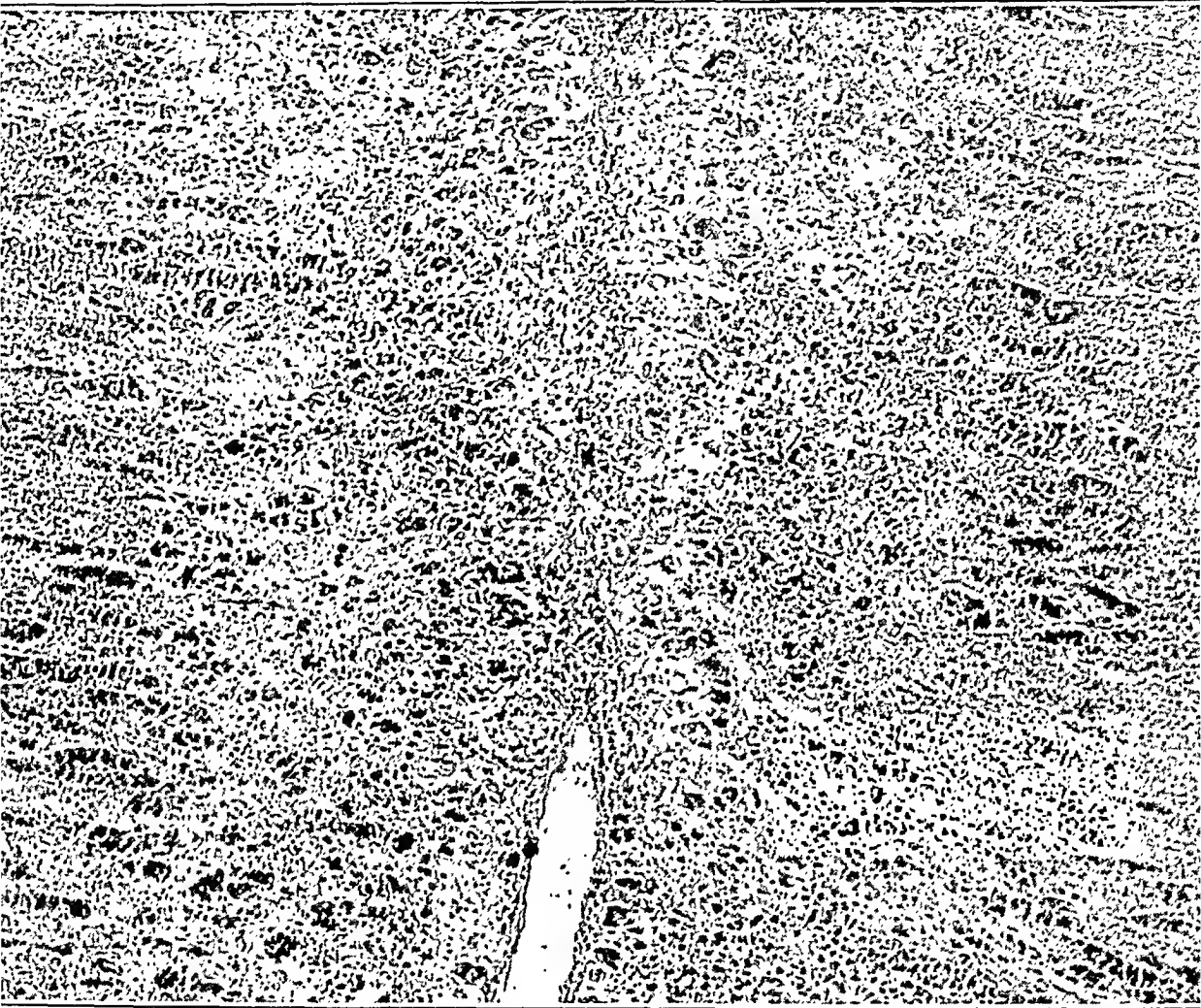


Fig. 8 (case 5).—Section of adrenal gland showing extensive degeneration of cells in inner zone of cortex. $\times 50$. (United States Army Medical Museum negative 87505.)

The spleen (weight 320 Gm.) showed many infarcts. On microscopic examination thrombi were seen in many arteriolar lumens.

The kidneys weighed 200 Gm. each. The capsule stripped with some difficulty, tearing off particles of tissue. On the cut surface the cortex was pale tan; the structural details were somewhat blurred, but the demarcation between the cortex and the pyramids was distinct. The histologic sections showed ischemic glomeruli and distention of Bowman's capsules and the tubules with fuzzy eosinophilic debris.

Some of the tubules contained compact hyaline casts, and the tubular epithelium was flattened. The capillaries in the pyramids were congested.

The adrenal glands showed no gross hemorrhages. A brown zone was noted between the gray medulla and the bright yellow cortex. Microscopic examination revealed a zone of degeneration involving the reticular and inner fascicular layers (fig. 8). There were marked disruption and fragmentation of the cords. The individual cells were shrunken, with frayed cell outlines, and the cytoplasm was scanty and impregnated with fine and coarse brown pigment. In many places only a small amount of cellular debris and a delicate reticular stroma were seen. The

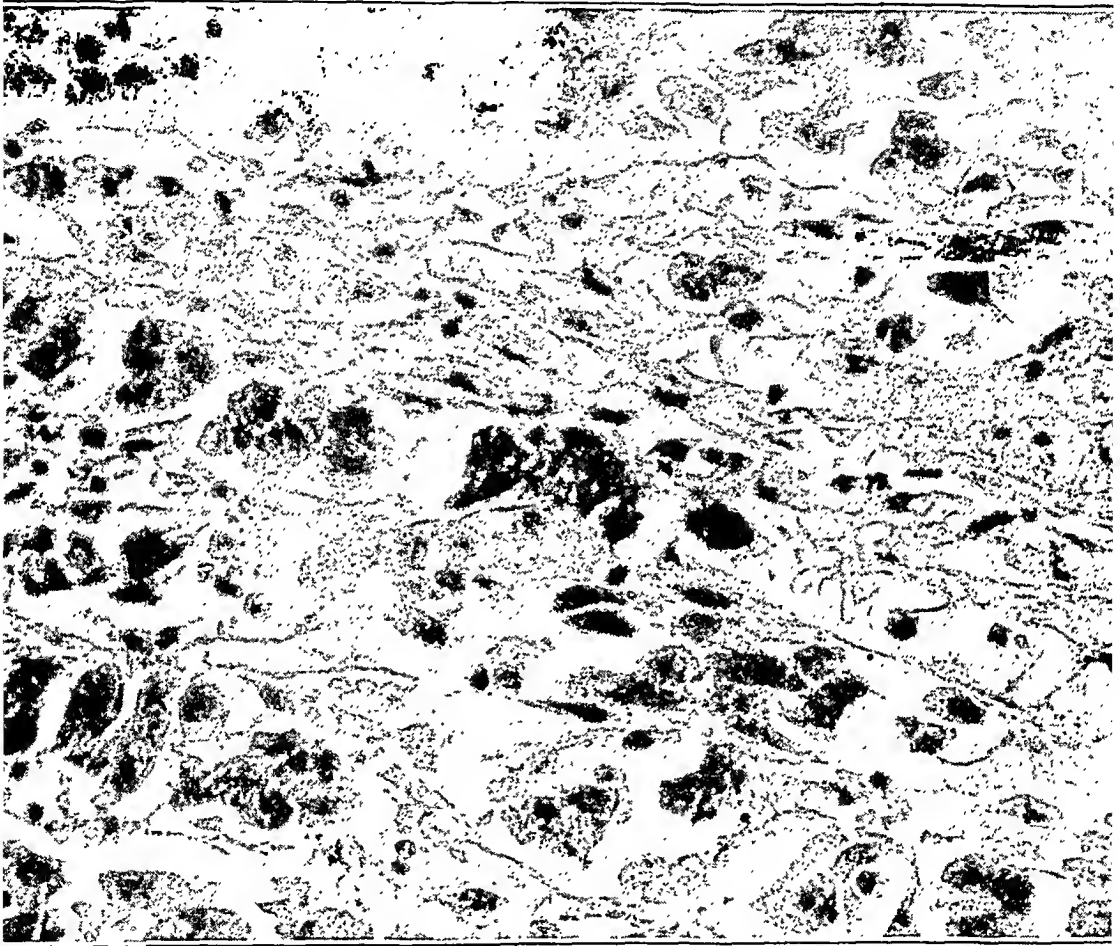


Fig. 9 (case 5).—Section of inner zone of adrenal cortex showing in greater detail the degeneration of the cells. $\times 500$. (United States Army Medical Museum negative 87620.)

cells in the external layers of the cortex were shrunken and presented a solid homogeneous cytoplasm. There was also evidence of "tubular" degeneration although much less conspicuous than in the previous case. The "tubular" changes of the outer fascicular layer were overshadowed by the disruption of the cords and the degeneration of the cells in the inner layers (fig. 9). The sinusoids, especially in the degenerated zone, were greatly distended and filled with blood, with a few escaped red blood cells visible outside their walls. The border zone between the degenerated and the external layers was infiltrated by lymphocytes

and occasional polymorphonuclear leukocytes. The medulla showed shrinkage of the individual cells, as well as foci of lymphocytic infiltration.

The leptomeninges were cloudy over both hemispheres of the brain and on microscopic examination revealed the typical changes of acute meningitis. The pituitary gland showed hyperemia of the anterior lobe.

CASE 6.—A 19 year old white soldier was admitted to the hospital at 10 a. m. on Dec. 3, 1944. On admission, he stated that he had had a "cold" for the preceding week, but thirty-five hours prior to admission he experienced some shaking chills and vomited. His temperature on admission was 99.2 F.; the pulse rate was 90, and the respirations were 18 per minute. Physical examination revealed essentially normal conditions except some slight injection of the pharynx. On December 4 at 9 a. m. there was a recurrence of the shaking chills and vomiting, which became increasingly severe. These were accompanied with malaise, vertigo and a generalized throbbing headache. His temperature (rectal) then was 103 F.; the pulse rate was 100, and the respirations were 20 per minute. At this time the chest exhibited scattered macular-rose spots of varying sizes, which were not painful and did not blanch on pressure. Slight injection of the pharynx was still noted. Other physical findings, including the neurologic ones, were normal. The blood pressure was 130 systolic and 80 diastolic. A leukocyte count was 18,150, with 81 per cent neutrophils, and a blood culture failed to show growth of any organism. A spinal puncture yielded clear fluid with normal dynamics and containing 35 cells per cubic millimeter, of which 94 per cent were neutrophils. A culture later yielded meningococci, group 1. A diagnosis of meningococcemia was made, and treatment with penicillin was begun. At noon on December 4, three hours later, the patient suddenly grew pale, weak, listless, sluggish and lethargic, and the blood pressure dropped to 120 systolic and 50 diastolic. The macules increased in size and number, many developing petechial centers, and other petechial lesions appeared. Huge macular blotches began to appear and disappear periodically over the entire body but mainly over the chest, the arms and the neck. Cyanosis was present. The Kernig and great toe reflexes became positive. Stupor and coma ensued. Retention of urine developed, followed by incontinence. A catheterized specimen showed sugar (3 plus) but no acetone or diacetic acid. Chemical analysis of the blood revealed nonprotein nitrogen 45 mg. and sugar 266 mg. per hundred cubic centimeters, but the chlorides, the carbon dioxide-combining power and the creatinine were within normal limits. Nuchal rigidity became noticeable. The temperature climbed to 104 F.; the pulse became feeble and imperceptible; the respirations rose to 28, and the blood pressure dropped to 100 systolic and 40 diastolic. Spinal puncture at this time showed a cloudy fluid, under moderately increased pressure, with 9,000 cells per cubic millimeter, of which 94 per cent were neutrophils. Insulin was added to the routine therapy. The patient's condition remained precarious until 9 a. m., December 5, when definite improvement was noted. On the morning of December 7 the patient was rational, and improvement was apparent. Convalescence from this point on was steady, and recovery was complete.

CASE 7.—An 11 month old boy was dead on arrival at the hospital on Dec. 19, 1944. A fragmentary history was obtained from his parents of a mild acute infection of the respiratory tract beginning three days before admission. A rash, described by his mother as "little red bumps under the skin," appeared on December 17, but the general condition of the child did not appear alarming to the parents until December 18, when a high fever developed. The rash assumed a dark color

and began spreading rapidly. The child apparently died on his way to the hospital, three days after the onset.

Meningococci group 2 A were later recovered from blood taken for culture at autopsy.

The autopsy was performed fifteen hours after death. The patient was well developed and well nourished. The skin was covered with a macular purpuric rash consisting of irregularly shaped, deep purple blotches scattered over the entire body but more pronounced over the face, the shoulders and the extremities



Fig. 10 (case 7).—Section of adrenal gland showing hemorrhage in inner zone and "tubular changes" in outer zone. $\times 50$. (United States Army Medical Museum negative 87498.)

while relatively inconspicuous over the chest, the abdomen and the back. The central portion of some of the macules was a pale yellowish gray, while the outer portion consisted of a distinct dark hemorrhagic zone, which faded gradually into the surrounding skin. The hemorrhagic discoloration extended into the corium. Sections of the skin revealed arteriolar thrombi in the corium and in the superficial layer of the subcutaneous fat, with patches of a diffuse infiltration of polymorphonuclear leukocytes in the corium and epidermis above the thrombosed

vessels. Bacterial stains revealed the presence of gram-negative intracellular diplococci.

The viscera apart from the adrenal glands were not remarkable except for slight congestion and patchy edema of the lungs and some congestion of the hepatic sinusoids. There was also a diffuse sprinkling of polymorphonuclear leukocytes throughout the hepatic tissue.

Both adrenal glands showed diffuse hemorrhagic discoloration of the parenchyma. Microscopic examination revealed diffuse hemorrhages involving especially the inner cortical layers (fig. 10). The sinusoids were congested, and the cortical

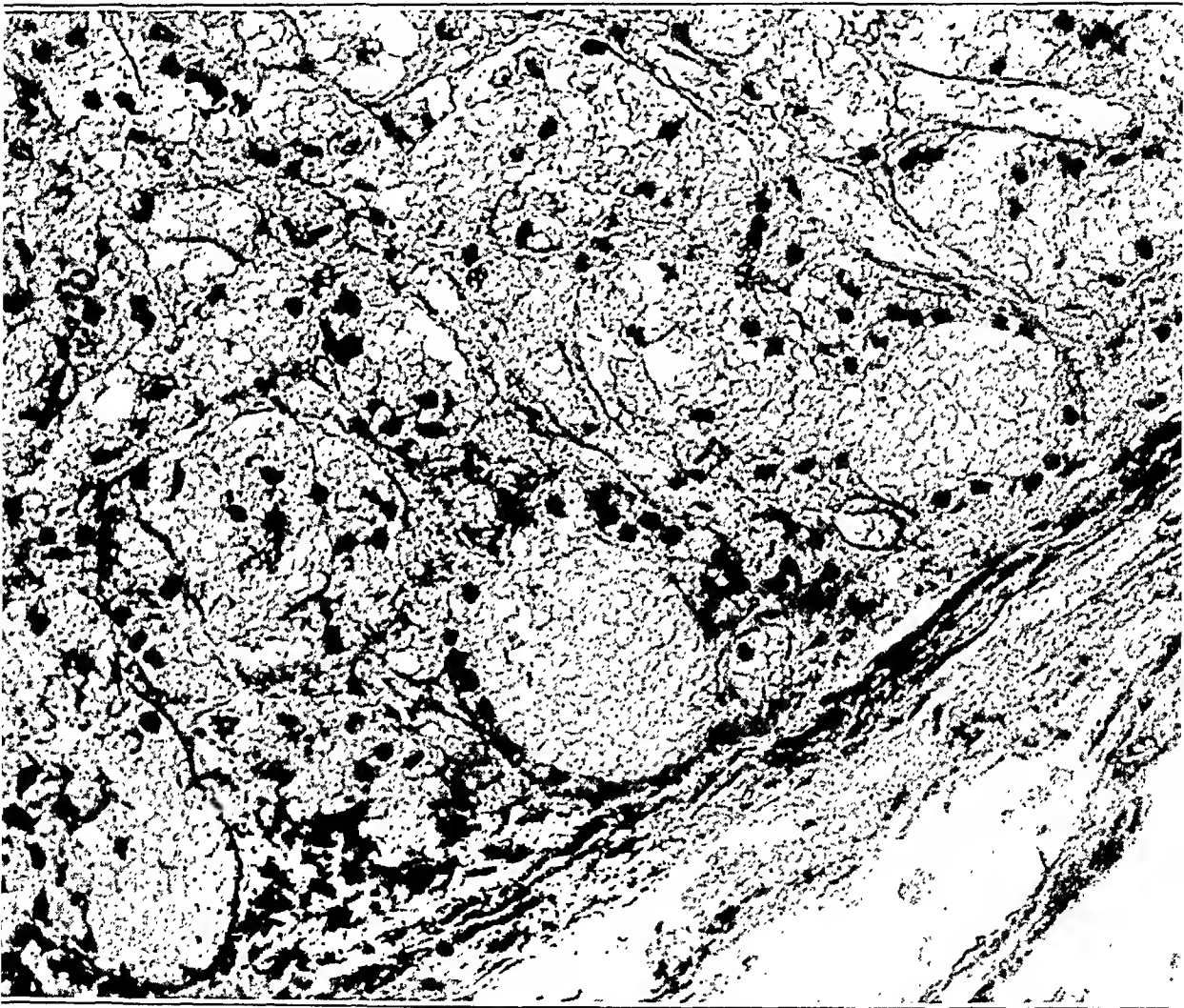


Fig. 11 (case 7).—Section of external layer of adrenal cortex showing detail of "tubular changes." The lumens are packed with escaped red blood cells. Some of the epithelial cells appear flattened, and others are missing. $\times 450$. (United States Army Medical Museum negative 87495.)

tissue was composed of cells with solid or finely vacuolated cytoplasm. Here also "tubular" changes were observed in a few instances in which small islands of cortex escaped flooding with blood. At some points, even in the hemorrhagic areas of the glomerular zone, the glomerular structures assumed a circular arrangement resembling a cross section of a tubule, with flattened adrenal cells forming the lining, the lumen being tightly packed with red blood cells (fig. 11). In some

isolated instances the lining cells were missing entirely, while in others they displayed degenerative changes.

The meninges did not reveal any conspicuous lesions grossly, but microscopically there was a moderate amount of inflammatory cellular infiltration in which polymorphonuclear leukocytes, large monocytes and a few lymphocytes participated.

NOTE.—All the cranial, thoracic, abdominal and pelvic viscera were examined grossly in each autopsy. Histologic sections of the following organs were prepared and examined: skin, heart, aorta, lungs, liver, pancreas, spleen, lymph nodes, thymus and adrenal and pituitary glands. Sections of the trachea, the gastrointestinal tract, the gallbladder, the prostate, the bladder, muscle, bone marrow and the thyroid gland were prepared only if the gross appearance of the tissues suggested a deviation from normal. Sections of the pituitary gland were missed in case 2, of the thymus and lymph nodes in case 5 and of the aorta and spleen in case 7. For the sake of brevity only the deviations from gross and microscopic normal appearance are reported in the preceding pages.

COMMENT

For many years various diseases have been reported under the term "Waterhouse-Friderichsen syndrome." These have included not only meningococcic but also other infections, acute purpuras and not infrequently diseases in which the cause was undetermined, though latterly the expression has tended to become synonymous with fulminating meningococcic infections. In many instances postmortem examinations either were not made or else failed to reveal adrenal hemorrhage, and in a few cases the patient survived, yet the illness was still so labeled. Obviously the term is erroneously applied under such circumstances, for the one common denominator in the cases reported by both Waterhouse and Friderichsen was massive adrenal hemorrhage. Since it is inconceivable that a patient can long survive after his adrenal glands have been destroyed, it follows that the diagnosis is essentially a pathologic one and that it should be reserved exclusively for those patients in whom adrenal hemorrhage is demonstrated—if, indeed, it is to be used at all. Certain recent publications⁷ indicate that there is already developing a tendency to regard this matter in a similar light.

If one wishes to continue to use the term "Waterhouse-Friderichsen syndrome," then cases 1, 3 and 7 certainly fall within that category, inasmuch as the one cardinal and pathognomonic criterion of that condition, extensive adrenal hemorrhage, was present; also, they exhibited another, near cardinal sign, hemorrhagic cutaneous phenomena. By the same criterion, cases 2 and 5 cannot be properly included, inasmuch as massive adrenal hemorrhage was not present, nor cases 4 and 6, because the patients survived and hence the condition of their adrenal

7. (a) Pratt-Thomas, H. R.; Kelley, W. H., and Gazes, P. C.: Fulminating Meningococcemia (the Waterhouse-Friderichsen Syndrome), *South. M. J.* **38**: 229-235 (April) 1945. (b) Adams, F. D.: Some Clinical Aspects of Meningococcic Infection, *Ann. Int. Med.* **20**:33-44 (Jan.) 1944.

glands was not known. But all 7 of these patients did have two things in common: a proved meningococcic infection and a fulminating clinical course. Hence they are all properly labeled as instances of "fulminating meningococcic septicemia."⁸

In the 2 patients in whom autopsy revealed the absence of massive adrenal hemorrhage, there were, nevertheless, adrenal changes consisting of zonal degeneration and severe congestion; moreover these were located in the same layers where in the other 3 cases the intensity of the hemorrhagic changes was most striking. Pathologically, therefore, there were essentially two types of adrenal changes: degenerative and hemorrhagic. The degenerative changes consisted in disruption of the cortical cords, death and lysis of individual cells and congestion and edema of the stroma, involving the entire reticular and the inner half of the fascicular zones (figs. 2, 4, 8 and 9). The outer fascicular and glomerular layers presented channeling of the adrenal cortex cords resulting in the formation of "tubules" (figs. 2 and 3). The hemorrhagic phenomena were most intense in the same areas where the degenerative changes were most pronounced in the first group (fig. 1), but they extended also into the medulla and into the external layers of the cortex where leaking of blood into "tubular" lumens (fig. 7) or packing of the lumens with extravasated blood (fig. 11) was evident. The clinical course of patients presenting the degenerative lesions was not essentially different from that of patients showing the hemorrhagic. It seems logical to believe that these two types of changes are stages in the same process, the first representing an early, probably still reversible phase and the latter the terminal, irreversible phase.

The cause of the circulatory collapse, which is such an outstanding phenomenon in this disease, has been the subject of much speculation. It seems unreasonable to place the entire blame on the exhaustion of hormonal supply associated with the adrenal lesions, even though the latter are usually of a high degree, as they were in the fatal cases reported here. In certain instances, injuries of other organs may be responsible to a greater or less degree: In case 5, for example, there was severe injury of the myocardium, and other conditions observed in this case (pulmonary edema and bilateral hydrothorax) were consistent with circulatory failure of cardiac origin. Meningeal inflammatory changes can scarcely be held responsible for the collapse, for although they were invariably present in all the cases yet they did not appear to be so extensive and so intense as in other fatal cases of frank meningococcic meningitis seen by us. The other pathologic developments, such as focal hepatitis, splenic infarcts and the congestive phenomena of various

8. The term "meningococcic septicemia" is used rather than "meningococcemia" to lend emphasis, by the use of the word "septicemia," to the existence of sepsis, or poisoning.

organs, were no more pronounced than they usually are in acute septicemias in general. It seems probable that in these fulminating infections no one organ or system of the body can be said to be injured so severely as to be by itself entirely responsible for the circulatory failure.¹ This is not to say, however, that the deprivation of the body of the normal adrenal hormonal supply may not play some part in its genesis. In discussing the role of the "tubular changes" in the adrenal glands, Rich⁶ stated that these lesions may "be at least a contributing factor in some of the instances of circulatory collapse that occur during severe acute infections." This point of view seems reasonable, and it is probable that the cause of the collapse is primarily a widespread injury of many tissues as a result of the toxic action of the bacterial products; the adrenal glands share in this injury, and the physiologic disturbances ensuing therefrom play a part, but only a part, in the resulting catastrophe. This point of view is supported by the work of Ebert and Stead,⁹ who, after studying the nature of the shock accompanying acute infections, came to the conclusion that it does not have the same mechanism as hemorrhagic or traumatic shock because the volume of plasma is not decreased and transfusions are not beneficial; nor is it due to a diminished venous return to the heart from pooling in the small vessels, because filling the venous system does not improve the circulation.

There is another factor which theoretically may play a role in the circulatory collapse, either directly by its influence on metabolism in general or indirectly through the part it plays in adrenal metabolism—vitamin C. It is known that this vitamin is particularly abundant in the adrenal glands and that in acute infections its concentration in the body rapidly diminishes.¹⁰ It has been observed that its oral or parenteral administration in cases of Addison's disease may strikingly diminish the pigmentation and that in 3 patients with Addison's disease there was a definite parallelism between the degree of vitamin C deficiency and the severity of the disease.¹⁰ Although no data bearing on its metabolism in fulminating meningococcemia have been encountered, the possibility that it may be involved in the collapse is worth mentioning, and it is suggested that it would be worth while in the future to administer large doses of ascorbic acid to patients with this disease.

In attempting to interpret the pathologic physiology of the adrenal glands in this illness several factors may be considered. Normally, the adrenal cortical cells, especially in the outer layers, are filled with

9. Ebert, R. V., and Stead, E. A., Jr.: Circulatory Failure in Acute Infections, *J. Clin. Investigation* 20:671-679 (Nov.) 1941.

10. Bicknell, F., and Prescott, F.: *The Vitamins in Medicine*, London, William Heineman, Ltd., 1942, chap. 6, p. 300.

lipoid globules, which when viewed microscopically after fixation and dehydration appear as vacuoles. It is generally believed that this lipid either contains the hormone or is the substance from which it is derived and that this globular state represents a storage phenomenon.¹¹ Now, experimental work and pathologic observation have demonstrated that not only in animals subjected experimentally to various metabolic disturbances¹² but also in persons with overwhelming infection and cachexia¹³ there is a pronounced diminution of the lipid content of the adrenal cortex. The lipid material is supposedly released into the circulation,¹¹ and the cells then degenerate, their cytoplasm changing from its normal globular to a more homogeneous or granular state.¹⁴ These changes were obvious in cases 3 (fig. 7) and 5 (fig. 8), and in the others they were suggested in the preserved islets of cortical cells between the hemorrhagic areas, although largely obscured by the hemorrhage itself (fig. 11).

The cortical cell originates in the outer layer of the cortex, and as it ages it travels centripetally, eventually undergoing degeneration, death and lysis in the innermost layer. This process is a slow and orderly one, and regeneration of new cells preserves the integrity of the tissue. The degeneration of the cell in the reticular layer is, then, a normal phase—the final one—of the cell's life cycle. It has been demonstrated that an acute infection increases the demand on the adrenal cortex, thus bringing about the cytoplasmic changes described.¹¹ If the infection becomes overwhelming, as in fulminating meningococcemia, the demand is still further increased, so that the natural aging process of the cell is accelerated beyond the natural regenerative capacity of the tissue to replace it. As a consequence the cell dies before reaching its normal site of lysis. Its death in the outer layer permits serum to escape through the vacancy which it leaves; hence channeling or "tubule" formation results, while the death of many (older) cells in the deeper layers results in the creation of a wide zone of degeneration involving the inner half of the cortex. This zone now becomes a locus minoris resistentiae due to extensive loss of support to the walls of the sinusoids. This factor, combined with a systemic increase in capillary permeability resulting from the infection, may explain the occurrence of hemor-

11. Zwemer, R. L.: A Study of Adrenal Cortex Morphology, *Am. J. Path.* **12**:107-114 (Jan.) 1936.

12. Sarason, E. L.: Morphologic Changes in the Rat's Adrenal Cortex Under Various Experimental Conditions, *Arch. Path.* **35**:373-390 (March) 1943.

13. Sarason, E. L.: Adrenal Cortex in Systemic Disease, *Arch. Int. Med.* **71**: 702-712 (May) 1943.

14. Maximow, A., and Bloom, W.: A Text Book of Histology, Philadelphia, W. B. Saunders Company, 1930.

rhages in some cases of fulminating meningococcemia. Also, the loss of individual cells in the outer layers of the cortex permits blood cells to be extravasated into the "channel." The process may be aided by the postural factor in a patient with failing circulation, lying prone on his back, as the blood pools in the dependent parts of the body, which would include the adrenal glands. Of course, it is possible that the actual hemorrhage may be simply a terminal condition, having little or no causal relationship to the production of death.

This concept, then, of the course of events in these patients is that the picture is, from beginning to end, one of overwhelming septicemia with acute vasomotor collapse. Among others, adrenal changes occur, consisting at first in degenerative phenomena manifested by "tubular" degeneration in the outer cortical layers with more pronounced lesions in the inner zones. Lysis of many of the individual cells follows, resulting in disruption of the cords. Engorgement and edema follow to replace the vacuum and to dispose of the debris left from the degenerative process. It is assumed that at this stage the adrenal changes are reversible and the patient may recover (the recoveries of the patients in cases 4 and 6 probably exemplify this), or the infection may be so overwhelming that the patient may die nevertheless before adrenal hemorrhage has had a chance to occur (as in cases 2 and 5), or adrenal hemorrhage may result, following which recovery is impossible (cases 1, 3 and 7). This interpretation would explain the variation in the pathologic observations of the reported cases as well as the recoveries from fulminating meningococcic septicemia.

So far as the pathogenesis of the rash is concerned, the purpuric component is probably due to loss of tonus with consequent congestion in the corium, which, in conjunction with increased capillary permeability, results in rupture and hemorrhage; the petechial component is probably due to the presence of thrombi in the arterioles beneath the corium (as noted in cases 5 and 7); the periodically appearing and disappearing macular blotches (noted in case 6), to fluctuations in vasomotor tone, and the cyanosis of dependent parts, simply to peripheral vasomotor collapse with venostasis.

It has been observed that meningococcic infections are not infrequently accompanied with transient glycosuria and/or acetonuria.¹⁵ In a review of 125 cases at this hospital it was found that in 12 the patients showed transient glycosuria. Of the 7 patients with fulminating infection here reported on, 2 had significant amounts of sugar in the urine while 4 had at least one blood sugar level higher than 120 mg. per

15. Ferguson, F., and Barr, D.: Glycosuria in Meningitis, *Ann. Int. Med.* **21**: 173-186 (Aug.) 1924.

hundred cubic centimeters. The elevation was not marked in 2 of these, but in 1 (a survivor, case 6) it was 266 mg. per hundred cubic centimeters. The pancreas and the pituitary gland were studied in all but 1 of the cases brought to autopsy, with the problem of this hyperglycemia in mind, but they showed no significant changes in any instance; however, the hypothalamic areas were not studied at all. In 1 patient (case 5) with a blood sugar content of 147 mg. per hundred cubic centimeters the liver did show some changes, with congestion of the central sinusoids and some areas of infiltration of the portal spaces; however, it is doubtful that the changes were intense enough to be responsible for any significant disturbances of the carbohydrate metabolism. This study can furnish only conclusions of a negative nature concerning the cause of the disturbance.

It is important to emphasize the fact that when first seen these patients often appear to be suffering from nothing more than an ordinary infection of the respiratory tract. Insufficient stress has been laid on this point by most writers. An exception is Adams,^{7b} who does call attention to it and who has written a vivid description of the characteristic clinical picture in this disease. Of the 7 patients reported on here, 4 were initially admitted to respiratory disease wards. In this hospital every new officer, on being assigned to such a ward, is cautioned to be on the alert for these cases. Frequent inspection of the entire body for eruptions is an essential for early diagnosis.

The principles of treatment in fulminating meningococcemia are:

- (a) To combat the infection, with sulfadiazine or penicillin or both.
- (b) To combat shock, with adrenal cortex extract, epinephrine, plasma and sodium chloride.
- (c) To combat anoxemia, with oxygen.
- (d) To combat special complications as they arise (as hyperglycemia, with insulin).

An analysis of the data in this report (table 7) fails to uncover any one factor to which recovery may be attributable. For instance, the largest dose of penicillin per hour was given in a fatal case; likewise, while one recovered patient received 116 cc. of adrenal cortex extract during the period of acute illness, the other received only 2 cc., and a patient in 1 of the fatal cases was given 40 cc. The only fact which is suggestive in the present data is that both the recovered patients were given 500 cc. of plasma, while in the fatal cases one patient received none and the other only 250 cc. In view of the lack of any evidence of hemoconcentration in the 3 patients on whom studies were made and of the experimental evidence that in cases of acute infections the volume of plasma is not decreased,⁹ it seems probable

that the recovery of the 2 patients who had plasma was coincidental and not due to the plasma. The question as to whether adrenal substitution therapy is of value cannot be answered by this study. The theory has been advanced that antitoxic serum might have a definite place in therapy,¹⁶ but it was not used in any patient in this series. The idea that ascorbic acid may be beneficial has been presented earlier in this paper. A proper evaluation of therapy would ideally depend on a plan of treating a number of patients identically except for a variation of only one factor at a time in different groups. However, the infrequency of the disease and the fact that only an occasional patient recovers make such a plan totally out of the question. The ultimate evaluation of the best treatment for this disease will probably have to rest on a statistical analysis of the therapy in the reported survivals in comparison with that in the fatal cases. Meantime, it would seem that the main effort of therapy should be directed, early and vigorously, toward overcoming the infection and the toxemia, with supportive measures occupying a secondary though not unimportant place, in the hope that the patient will thereby be given a chance to recover before irreversible changes, such as hemorrhages, occur in the adrenal glands.

SUMMARY AND CONCLUSIONS

The confusion surrounding the use of the term "Waterhouse-Friderichsen syndrome" is pointed out, and it is suggested that it either be abandoned entirely or else be rigidly restricted to those patients presenting the clinical picture of an acute fulminating febrile disease and in whom adrenal hemorrhages are found post mortem. Acute septicemias of proved cause should be called "fulminating septicemia."

Seven cases of proved fulminating meningococcic septicemia are reported, in which 2 patients recovered. The clinical and pathologic observations are presented in detail.

In the beginning the illness was usually diagnosed as an ordinary infection of the respiratory tract. An eruption developed within three to twenty-four hours after the onset, the rash appearing in the form of erythematous macules, petechiae, purpura or a simple erythematous blush, usually in combination. Signs of shock appeared in twelve to twenty-four hours. Symptoms suggesting meningitis were usually present: Five of the 7 patients had an increased number of cells in the spinal fluid, pleocytosis developing under observation in 3 patients; cultures of the spinal fluid of the same 5 patients yielded the menin-

16. Boger, W. P.: Fulminating Meningococcemia: Demonstration of Intracellular and Extracellular Meningococci in Direct Smears of Blood, *New England J. Med.* **231**:377-404 (Sept. 14) 1944.

gococci. Cultures of the blood of 5 patients were positive for meningococci. Albuminuria and azotemia were the rule, and hyperglycemia was present in 4 of the 5 patients on whom a dextrose tolerance test was made; none of the patients showed significant acidosis. In no instance was hemoconcentration discovered.

In 3 of the fatal cases adrenal hemorrhage was shown, while in the other 2 adrenal changes were present, consisting of zonal degeneration and conspicuous congestion in the inner layers of the cortex, with "tubular changes" in the outer layer. In 1 case there were myocardial changes which were sufficient to have caused a circulatory collapse, but in the others there were no significant changes apart from those in the adrenal glands. It is believed that the cause of the circulatory collapse is the effect of the bacterial poisons on all the tissues of the body. In this the adrenal glands play a part but only a part; they are not wholly responsible for the collapse. It is suggested that in addition to the toxic effect of the poisons and the diminution of the adrenal hormone supply a depletion of vitamin C may be a factor.

The theory is advanced that the changes in the adrenal glands can be accounted for as follows: The increased demand on the adrenal glands, as a result of the infection, depletes the cortical cells of their lipoid (hormone-containing) material; the cells degenerate more rapidly than normally, producing the "tubular" pattern in the outer layers and more conspicuous lesions in the inner layers, with eventual lysis of many of the cells before they have reached their usual site of death; this stage is considered reversible. Later, as a result of the loss of support of the sinusoids because of the premature death of the cortical cells, rupture and hemorrhage may occur—an irreversible stage. The patient may die before hemorrhage occurs.

The primary aim of treatment is to overcome the infection. In addition to the supportive measures usually advocated, it is suggested that, on theoretic grounds, ascorbic acid might be of benefit.

APPENDIX

DETAILS OF THERAPY

CASE 1.—No details on record.

CASE 2.—Penicillin: 30,000 units at 10 a. m., 100,000 units by intravenous drip at 10:30 a. m. and 20,000 units at 1:30 p. m. on January 23.

Sulfadiazine: 4 Gm. by mouth at 6:30 and 9:45 a. m. and 3 Gm. intravenously at 1:30 p. m. on January 23.

Adrenal cortex extract: 20 cc. at 10:30 a. m. on January 23.

CASE 3.—Sulfadiazine: 5 Gm. intravenously at 1 p. m. on March 13.

Adrenal cortex extract: 30 cc. at 1 and 10 cc. at 1:30 p. m. on March 13.

Epinephrine hydrochloride, aqueous solution (1:1,000): 1 cc. at 2:06 p. m. on March 13.

CASE 4.—Penicillin: 40,000 units at 9:30 a. m., 100,000 units at 10:15 a. m. and 25,000 units at 4 p. m. on March 29; 25,000 units at 12, 12:45 and 3 a. m. on March 30, and thereafter every 3 hours day and night until 6 a. m. on April 3.

Sulfadiazine: 7 Gm. intravenously at 9:15 a. m. on March 29; 2 Gm. at 4 p. m. and 1 Gm. intravenously at 7:45 p. m. on March 30; 2 Gm. subcutaneously at 12 and 4 a. m. and 1.5 Gm. by mouth at 10 a. m. and 6 p. m. on March 31; 1.5 Gm. at 2 a. m. on April 1, and thereafter 1.5 Gm. every 4 hours, day and night until 4 p. m. on April 15.

Adrenal cortex extract: 30 cc. at 8:30 a. m., 10 cc. at 9:30 and 11 a. m. and at 2, 8 and 11 p. m., and 6 cc. at 5 p. m. on March 29; 10 cc. at 5 and 11 a. m. and 2 and 5 p. m. on March 30 and 31 and April 1, and beginning at 2 a. m. on April 2, 10 cc. every 4 hours, day and night until April 7.

Desoxycorticosterone: 10 mg. at 10:30 a. m. on March 29.

Epinephrine hydrochloride, aqueous solution (1:1,000): 1 cc. at 8:50 and 9:15 a. m. and 2:15 and 4:50 p. m. on March 29 and 0.5 cc. intravenously at 12 a. m. on March 30.

Epinephrine in oil (1:500): 1 cc. at 11 a. m. on March 29 and 1 cc. at 12:10 a. m. and 4 and 6 p. m. on March 30.

Plasma: 500 cc. at 11:40 a. m. on March 29.

CASE 5.—Penicillin: 40,000 units at 8:45 a. m., 100,000 units intravenous drip at 10 a. m. and 25,000 units at 3, 6 and 9 p. m. on April 14, and 25,000 units at 12, 3, 6 and 9 a. m. and 12, 3 and 6 p. m. on April 15.

Sulfadiazine: 5 Gm. intravenously at 6 p. m. and 2.5 Gm. subcutaneously at 8:30 p. m. on April 13, 2.5 Gm. subcutaneously at 4:30 a. m. and 2 Gm. intravenously at 9 a. m. on April 14.

Adrenal cortex extract: 30 cc. at 8:30 a. m. and 10 cc. at 10:30 a. m. and at 12:30, 3:30 and 5 p. m. on April 14, then every 2 hours, day and night through 7 p. m. on April 15.

Desoxycorticosterone: 10 mg. at 8:50 a. m. and 5 mg. at 10:30 a. m. on April 14.

Epinephrine hydrochloride, aqueous solution (1:1,000): 0.5 cc. at 9 a. m. on April 14.

Epinephrine in oil (1:500): 1 cc. at 12 and 7 p. m. on April 14 and at 3 and 11 a. m. and 7 p. m. on April 15.

Plasma: 250 cc. at 6 p. m. on April 15.

CASE 6.—Penicillin: 25,000 units at 11 a. m. and 12 p. m. and 40,000 units at 3, 6 and 9 p. m. on December 4; 40,000 units every 3 hours, day and night, beginning at 12 a. m. on December 5 and continuing through 9 a. m. on December 9; intrathecally, 10,000 units at 9:30 a. m. on December 5, and 7,000 units at 8:45 a. m. on December 6.

Sulfadiazine: 4 Gm. intravenously at 2 p. m., 2 Gm. intravenously at 6 p. m. and 1 Gm. subcutaneously at 10 p. m. on December 4; 1 Gm. at 2 a. m. on December 5; then 1 Gm. every 4 hours, day and night, until 10 a. m. on December 7, and then 1 Gm. every 6 hours until 8 a. m. on December 10.

Adrenal cortex extract: 2 cc. intravenously at 2:30 p. m. on December 4.

Epinephrine hydrochloride, aqueous solution (1:1,000): 1 cc. at 2:15 p. m. on December 4.

Epinephrine in oil (1:500): 1 cc. at 2:45, 4:30 and 8 p. m. on December 4 and at 4:30 a. m. on December 5.

Plasma: 500 cc. at 3:15 p. m. on December 4.

RHEUMATIC FEVER IN NAVAL ENLISTED PERSONNEL

II. Effectiveness of Intensive Salicylate Therapy in Cases of Acute Infection

COMMANDER R. C. MANCHESTER (MC), U.S.N.R.

ACUTE rheumatic fever in young adults either in naval service¹ or in civilian life² begins primarily as an acute infection exhibiting acute polyarticular arthritis as the major manifestation. The disabling character of the acute polyarticular manifestations results in early medical care in most instances, before irreparable visceral damage necessarily occurs or the chronicity of infection becomes fixed. Therefore, a therapeutic regimen which succeeds in modifying the natural course of the disease offers the opportunity of preventing these unfortunate sequelae. This paper deals with the effectiveness of intensive salicylate therapy by the Coburn technic³ in accomplishing these objectives.

The essential problems in the treatment of acute rheumatic fever are: the alleviation of acute articular, visceral and toxic manifestations; the prevention, or lessening of the degree, of permanent cardiac damage; the shortening of the over-all period of active infection and the prevention of relapses and residual chronic infection.

While there is no question that salicylates dramatically relieve the acute articular and toxic manifestations, most observations indicate that the benefits observed are due solely to the peculiar analgesic and antipyretic properties of salicylates rather than to a specific modifying effect on the course of the disease.⁴

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

1. Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel: I. An Analysis of the Major Manifestations Observed, the Factors Involved in Its Occurrence and the Cardiac Residua, *Arch. Int. Med.* **77**:317-331 (March) 1946.

2. Cohn, A. E., and Lingg, C.: The Natural History of Rheumatic Cardiac Disease, *J. A. M. A.* **121**:1-8 (Jan. 2) 1943.

3. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever: Rational Technique, *Bull. Johns Hopkins Hosp.* **73**:435-464 (Dec.) 1943.

4. (a) Hanzlik, P. J.: Action and Uses of Salicylates and Cinchophen in Medicine, *Medicine* **5**:197-371 (Aug.) 1926. (b) Swift, H. F.: Rheumatic Fever,

(Footnote continued on next page)

Master and Romanoff ^{4d} compared 33 patients with acute rheumatic fever who received 8 to 10 Gm. of sodium salicylate daily with 30 patients who received no antirheumatic drugs. The incidence and the degree of visceral manifestations and permanent cardiac damage were identical in the two groups. Polycyclic relapses occurred as frequently in one group as in the other, and the duration of active infection was uninfluenced.

Swift ^{4b} observed that subcutaneous nodules may appear continuously in patients receiving "maximum salicylate dosage." On the basis of biopsy studies of periarticular tissue, ⁵ he concluded that salicylates tend to control the acute exudative joint and periarticular tissue reactions but fail to suppress the submiliary proliferative lesions characteristic of the less acute phase and responsible for much of the permanent cardiac damage.

Coburn's ³ recent results utilizing intensive salicylate therapy are diametrically opposed to the preceding observations. Patients with acute rheumatic fever were given 10 Gm. or more of sodium salicylate daily, either intravenously for seven to fourteen days followed by oral therapy or orally throughout the course of treatment. Treatment was continued until the blood sedimentation rate had remained normal for a period of two weeks. In none of a group of 38 patients treated by this method did valvular heart disease develop, while in 20 of 63 patients receiving only symptomatic therapy there developed physical signs of heart disease. In addition, the duration of active infection and the incidence of polycyclic relapses were materially reduced. Coburn expressed the opinion that plasma salicylate levels of 35 mg. per hundred cubic centimeters or higher will suppress rheumatic infection, prevent significant cardiac residua and shorten the duration of active infection.

CLINICAL MATERIAL AND METHODS

The group for study comprised 77 young men afflicted with acute rheumatic fever, all of whom exhibited acute polyarticular arthritis as the major incipient manifestation. Each patient exhibited a temperature of 100 F. or over and had acute articular and/or visceral manifestations when therapy was instituted in this hospital. Therefore, the less severe, spontaneously subsiding infections have, for the most part, been excluded.

The elapsed time between the onset of the acute illness and the institution of treatment in this hospital was from one to five days in 30 per cent, five to ten

Am. J. M. Sc. **170**:631-647 (Nov.) 1925. (c) Murray-Lyon, R. M.: Salicylates in Rheumatic Fever, *Edinburgh M. J.* **43**:84-89 (Feb.) 1936. (d) Master, A. M., and Romanoff, A.: Treatment of Rheumatic Fever Patients With and Without Salicylates: Clinical and Electrocardiographic Study, *J. A. M. A.* **98**:1978-1980 (June 4) 1932.

5. Swift, H. F.: Pathogenesis of Rheumatic Fever, *J. Exper. Med.* **39**:497-508 (April) 1924.

days in 31 per cent, ten to fifteen days in 25 per cent and fifteen to twenty-five days in 14 per cent. Ninety per cent of the patients were classified as having new infections and 5 per cent as having polycyclic recrudescences because of an antecedent attack within a period of one year, and 5 per cent had suffered from recurrent rheumatic fever with residual chronic pain in the joints between the acute attacks.

Fifty-four patients received intensive salicylate therapy patterned after the regimen laid down by Coburn.³ To 35 of them 10 Gm. of sodium salicylate in 1 liter of lactate Ringer solution or isotonic solution of sodium chloride was administered daily for four to ten days, followed by oral therapy. Nineteen additional patients received oral therapy throughout the course of treatment. Intravenous medication was begun at 9 a. m. and completed at 3 p. m., requiring six hours for administration. Oral medication consisted of from 10 to 12 Gm. of acetylsalicylic acid or sodium salicylate daily, usually in conjunction with 8 Gm. of sodium bicarbonate. It was given in equally divided doses each four hours and was continued until the erythrocyte sedimentation rate had been within normal limits for two weeks.

Twenty-three patients who received small quantities of salicylates for symptomatic relief of acute symptoms comprised the control group. In most instances those who exhibited prolonged infection received intensive therapy late in the course of observation.

The duration of active infection was based on the erythrocyte sedimentation rate, an oral temperature over 99 F., a shifting P-R interval of over 0.2 second and clinical evidence of active articular and visceral manifestations.

Cardiac murmurs were recorded as very slight, slight, moderate and loud. Mitral systolic murmurs were evaluated with the patient in the horizontal position and lying on the left side. Under these conditions, slight mitral systolic murmurs transmitted to or beyond the anterior axillary line may be expected in 4 per cent of healthy service personnel and murmurs of moderate intensity are not observed.¹ Data for patients with preexisting heart disease have been excluded.

Electrocardiograms were taken at weekly intervals. Deviations from normal were based on the criteria adopted by the American Heart Association. Erythrocyte sedimentation rates were determined twice weekly by the Cutler technic.

Patients were kept under observation in this hospital until the rheumatic infection was quiescent or until chronic infection had persisted for more than three months. The shortest period of observation was twenty-seven days, the longest two hundred and eighty-four days and the average sixty-six days.

RESULTS OF TREATMENT

A comparison of the results obtained in the intensively treated and in the control group has been made on the basis of temperature, articular manifestations, erythrocyte sedimentation rate, electrocardiographic and cardiac responses and the incidence of relapses and residua.

The temperature and articular responses are presented in table 1.

The average duration of fever was 2.6 days and of objective articular manifestations 2.8 days in the 54 patients receiving intensive therapy. The longest period of fever in any patient was eight days and of objective articular manifestations six days. Treatment was

equally effective whether instituted early or late in the first twenty-five days of acute illness. In striking contrast, average duration of fever in the control group was fifteen days and of objective articular manifestations twenty-six days. Fever recurred for sixty days and objective articular manifestations for one hundred and fifty-four days in 1 patient and articular manifestations for eighty days in another. Intensive

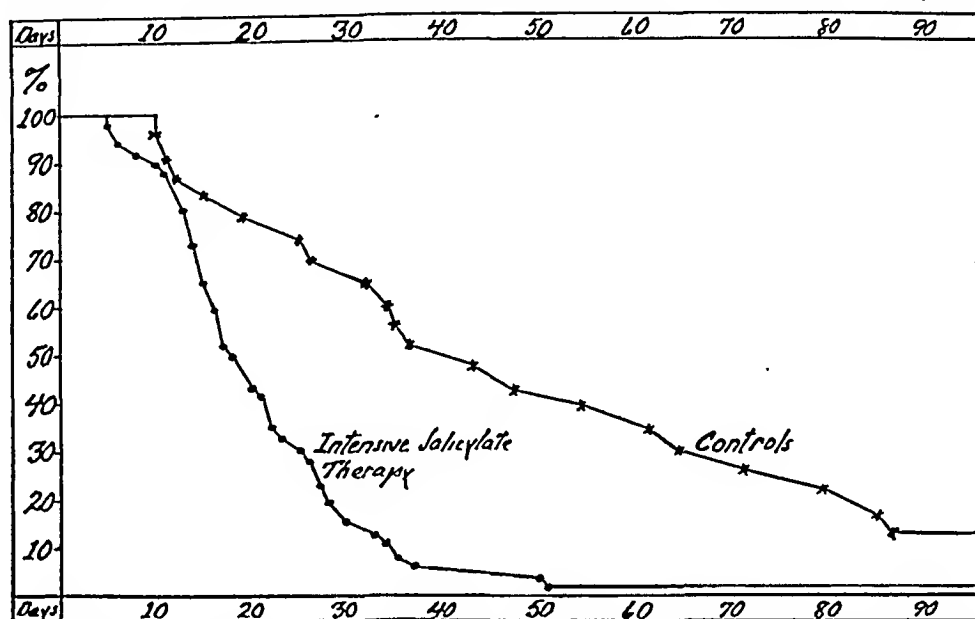


Chart 1.—The duration of elevated erythrocyte sedimentation rate in patients receiving intensive salicylate therapy and in the control group.

intravenous and oral therapy instituted late in these refractory cases was not particularly effective.

Erythrocyte sedimentation rate responses are represented graphically in chart 1. The erythrocyte sedimentation rate remained elevated for

TABLE 1.—The Average Duration in Days of Fever and of Objective Articular Manifestations in the Intensively Treated and in the Control Group

	Number of Cases	Average Duration in Days	
		Fever	Objective Articular Manifestations
Intensive salicylate therapy.....	54	2.6	2.8
Controls.....	23	15	26

more than ninety days in only 1 patient, or 2 per cent, of the group receiving intensive salicylate therapy, in contrast to a persistent elevation observed in 13 per cent of the control group. Excluding these patients, the average duration of elevated erythrocyte sedimentation rate was twenty days in the intensively treated patients and forty-two days in the controls. As shown in table 2, intensive therapy was

equally effective whether instituted early or late in the first twenty-five days of the acute illness.

Of the 54 patients receiving intensive therapy, treatment was instituted with salicylates intravenously followed by oral therapy for 35, while 19 received oral therapy throughout the entire course of

TABLE 2.—*Comparison of the Effectiveness of Intensive Therapy in Relation to the Duration of Elapsed Illness Before Treatment was Instituted*

Duration of Acute Illness	Number of Cases	Average Duration in Days		
		Fever	Objective Articular Manifestations	Elevated Erythrocyte Sedimentation Rate
1-5 days.....	16	2.7	2.8	19
5-10 days.....	14	2.4	2.7	21*
10-15 days.....	16	3.2	3.6	22
15-25 days.....	8	2.0	2.7	20

* One patient with persistent elevation of the erythrocyte sedimentation rate is excluded.

treatment. A comparison of the effectiveness of the two therapeutic regimens in alleviating fever and objective articular manifestations and suppressing elevation of the erythrocyte sedimentation rate is presented in table 3. The average duration of elevated erythrocyte sedimentation rate was twenty days, whether salicylate therapy was instituted intravenously or orally, while fever lasted a day longer and objective articular manifestations 1.1 days longer in the orally treated group. One patient started on intravenous therapy required 20 Gm. on the second and third days for complete relief of fever and articular signs.

TABLE 3.—*Effectiveness of Regimens Instituted by the Intravenous Route and of Those Consisting Entirely of Oral Therapy in Alleviating Fever, Objective Articular Manifestations and Elevated Erythrocyte Sedimentation Rate*

Administration of Salicylate	Number of Cases	Duration in Days		
		Fever	Objective Articular Manifestations	Elevated Sedimentation Rate
Intravenous followed by oral therapy.....	35	2	2.5	20
Oral therapy only.....	19	3	3.6	20

Three patients had recurrences of objective articular manifestations, and 1 other had a recurrence of fever and an increase in pericardial effusion after he was changed to oral therapy. Symptoms and signs promptly subsided in the former 3 patients with another course of salicylates intravenously. The latter patient was given 6 Gm. of aminopyrine daily instead of further salicylates intravenously, in order to avoid the excessive respiratory stimulation which often occurs in

patients with cardiac dyspnea.⁶ The acute symptoms promptly subsided and did not recur on subsequent salicylate therapy. This evidence in conjunction with clinical observations is interpreted as indicating that intensive regimens instituted orally are as effective in most instances as those utilizing salicylates intravenously but that in cases of severer refractory infections salicylates administered intravenously are required.

Signs of recognizable cardiac involvement in acute rheumatic fever consist of cardiac murmurs, clinical and roentgenologic evidence of enlargement, certain arrhythmias, electrocardiographic abnormalities, gallop rhythms and evidence of pericarditis. Slight and moderate mitral systolic murmurs, electrocardiographic abnormalities and pericardial friction rubs without effusion reflect incipient recognizable carditis which may or may not develop into a significant degree of cardiac damage. These signs were classified in this study as signifying "potential rheumatic heart disease." Diastolic and loud systolic murmurs, clinical and roentgenologic evidence of cardiac enlargement, gallop rhythms and pericardial effusion signify a serious degree of cardiac damage. They were classed as indicating "significant carditis" in the presence of active infection and as indicating "significant cardiac residua" after all evidence of active infection had subsided.

Levy and Turner⁷ found that salicylates hastened the recession of abnormal electrocardiographic tracings in rheumatic fever, while Carr and Reddick⁸ and Wyckoff, DeGraff and Parent⁹ observed that doses of salicylates as high as 8 Gm. daily were ineffective.

In this study 35 per cent of the patients receiving intensive salicylate therapy and 40 per cent of the controls exhibited electrocardiographic abnormalities. In chart 2 is presented graphically the duration of these abnormalities. On comparison of results in the two groups, it is apparent that electrocardiographic abnormalities subsided more rapidly in patients receiving intensive salicylate therapy than in the others, but the difference was not striking.

The cardiac manifestations at the termination of treatment in this hospital are presented in table 4. Of those patients who received

6. Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel: III. The Physiologic and Toxic Effects of Intensive Salicylate Therapy, *J. A. M. A.* **131**:209-213 (May 18) 1946.

7. Levy, R. L., and Turner, K. B.: Variations in Auriculo-Ventricular Conduction Time in Rheumatic Carditis with Salicylate Therapy, *Proc. Soc. Exper. Biol. & Med.* **25**:64 (Oct.) 1927.

8. Carr, J. G., and Reddick, W. G.: Conduction Disturbances in Acute Rheumatic Infections, *J. A. M. A.* **91**:853-856 (Sept. 22) 1928.

9. Wyckoff, J.; DeGraff, A. C., and Parent, S.: The Relationship of Auriculo-ventricular Conduction Time in Rheumatic Fever to Salicylate Therapy, *Am. Heart J.* **5**:568-573 (June) 1930.

intensive therapy, 71 per cent showed no residual cardiac stigmas; 15 per cent were classified as having potential rheumatic heart disease on the basis of a slight or moderate mitral systolic murmur; 7.4 per cent had had significant carditis when treatment was instituted, which cleared up completely, except in 1 patient who was left with a moderate mitral systolic murmur and was classed as having potential rheumatic

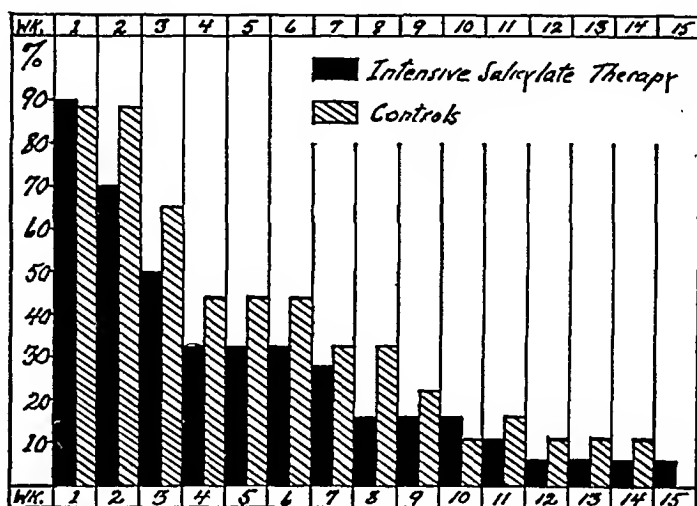


Chart 2.—The duration of abnormal electrocardiographic manifestations in patients of the intensively treated group and of the control group who exhibited such changes.

TABLE 4.—The Cardiac Status of the Intensively Treated Group and of the Control Group at the Time of Discharge From This Hospital

Therapy	Cardiac Status at Discharge					
	Normal Heart, per Cent	Potential Rheumatic Heart Disease, per Cent	Significant Carditis Clearing Up to		Significant Cardiac Residua, per Cent	Cardiac Deaths, per Cent
			Potential Heart Disease, per Cent	Normal, per Cent		
Intensive salicylate therapy	71	13	1.9	7.6	7.4	1.9
Control group.....	48	39	...	4.3	13	...

heart disease; 7.4 per cent suffered significant cardiac residua, and 1.9 per cent, or 1 patient, died of heart disease. The last patient had exhibited severe pancarditis and heart failure on admission and died on the fourth day of treatment. Significant carditis did not develop in a single patient who had not shown evidence of it before treatment was begun.

These results are in striking contrast to those in the control group, only 48 per cent of whom escaped with normal hearts. Thirty-nine per cent were classified as having potential rheumatic heart disease;

4.3 per cent had had significant carditis which cleared up and 13 per cent exhibited significant cardiac residua. Among the 3 patients with significant cardiac residua, only 1 showed evidence of cardiac involvement on admission to this hospital. It developed in the other 2 while they were under observation. In contrast, in none of the patients receiving intensive therapy did significant carditis develop after treatment was instituted.

TABLE 5.—*Cardiac Observations on Admission and at Discharge From This Hospital in Those Patients Who Exhibited Evidence of Significant Carditis*

Group	Patient	Cardiac Observations on Admission	Cardiac Observations at Discharge
Intensive salicylate therapy	V. M. A.	Massive pericardial effusion; electrocardiogram positive	First degree cardiac enlargement; moderate mitral systolic murmur transmitted to axilla
	C.	Massive pericardial effusion; electrocardiogram positive	Loud aortic diastolic murmur, moderately loud mitral systolic murmur transmitted to axilla; heart not enlarged
	D.	First degree cardiac enlargement; loud mitral systolic murmur transmitted to axilla; electrocardiogram positive	Loud mitral systolic murmur transmitted to axilla; no cardiac enlargement
	R. J. D.	Slight aortic diastolic murmur; loud mitral systolic murmur transmitted to axilla; electrocardiogram positive	Loud mitral systolic murmur transmitted to axilla; no cardiac enlargement
	N. D. E.	First degree cardiac enlargement; moderately loud systolic murmur transmitted to axilla; electrocardiogram positive	Moderate systolic murmur transmitted to axilla; no cardiac enlargement
	S. R. O.	Slight aortic diastolic murmur; moderate mitral systolic murmur	Normal
	C. D. E.	First degree cardiac enlargement	Normal
	B.	First degree cardiac enlargement; electrocardiogram positive	Normal
Control group	W. O. V.	Normal	Second degree cardiac enlargement; loud aortic diastolic murmur; loud mitral systolic murmur transmitted to axilla
	G. J. W.	Slight mitral systolic murmur; electrocardiogram positive	Loud mitral systolic murmur transmitted to axilla; middiastolic mitral murmur
	M. W. H.	Loud mitral systolic murmur transmitted to axilla; first degree cardiac enlargement	Loud mitral systolic murmur transmitted to axilla; moderate cardiac enlargement
	I. J. B.	Electrocardiogram positive; first degree cardiac enlargement after admission	Normal

Fifteen per cent of those receiving intensive therapy and 9 per cent of the controls exhibited significant carditis before treatment was begun in this hospital. Yet at the end of treatment the percentage was reversed, with only 7.4 per cent of the intensively treated patients suffering from significant residua in contrast to 13 per cent of the control group. An analysis of the cardiac observations on admission and on discharge is presented in table 5. Carditis progressed in the early phase of intensive therapy in some instances, but thereafter the

cardiac course was one of gradual improvement, and none of the patients suffered from progressive damage. Therefore the conclusion seems justified that already existing carditis was favorably influenced.

Two deaths occurred in the group of 54 patients receiving intensive therapy, while there were no fatalities in the control group. One death occurred on the fourth day, due to acute fulminating pancarditis. The other occurred on the seventh day, as a result of extensive rheumatic pneumonitis. The absence of fatalities in the 23 controls does not reflect dangers inherent in intensive salicylate therapy but, rather, reflects the fact that patients with milder disease were selected for the control group.

Polycyclic recrudescences of infection occur in between 20 per cent and somewhat under 50 per cent of young adults suffering from acute polyarticular rheumatic fever treated by rest in bed and sedation without antirheumatic drugs.¹⁰ In addition, the incidence of cardiac and other visceral manifestations increases with each relapse.^{10a} While recrudescences occurred in 22 per cent of the controls, the incidence was only 7.4 per cent in the 54 patients receiving intensive therapy. Only 1 of the 4 patients comprising the latter group showed an elevated erythrocyte sedimentation rate during the relapse. In none of them did recognizable cardiac or visceral manifestations develop, and their symptoms were promptly relieved by the resumption of salicylate therapy. The 22 per cent who exhibited recrudescences in the control group presented a less favorable picture. One had associated evidence of acute nephritis; one suffered from additional acute cardiac damage, and all 5 exhibited an elevation in the erythrocyte sedimentation rate.

The recognition of chronic residual infection presents a difficult problem. Subjective arthralgias and cardiac residua do not necessarily indicate active infection. In addition, systemic reactions to rheumatic infection are apparently modified in the intensively treated patients, as reflected by the fact that the erythrocyte sedimentation rate was elevated in only 1 of the 4 patients exhibiting polycyclic recrudescences while it was elevated in each of the 5 in the control group showing relapses.

Fifteen per cent of the patients receiving intensive therapy suffered from residual subjective arthralgias. One of these showed persistent elevation of the erythrocyte sedimentation rate, while 2 others suffered from pains in the joints of sufficient severity to indicate that active infection still existed. None of the 7.4 per cent exhibiting significant

10. (a) Graef, I.; Parent, S.; Zitron, W., and Wyckoff, J.: *Studies in Rheumatic Fever: I. The Natural Course of Acute Manifestations of Rheumatic Fever Uninfluenced by "Specific Therapy,"* *Am. J. M. Sc.* **185**:197-210 (Feb.) 1933.
(b) Master and Romanoff.^{4d}

cardiac residua showed evidence of chronic active infection, nor did they complain of residual arthralgias.

Twenty-six per cent of the control group complained of residual subjective arthralgias, with the erythrocyte sedimentation rate remaining elevated in 3 instances. One of these showed progressive cardiac damage in conjunction with chronic arthralgia, even after the erythrocyte sedimentation rate had returned to normal on the one hundred and twelfth day. None of the others exhibited significant cardiac residua, nor did any with significant cardiac residua exhibit chronic arthralgias except in the case mentioned. On the basis of the evidence presented, the incidence of chronic infection was regarded as 5 per cent in the intensively treated group and as 18 per cent in the controls. Furthermore, no relationship was found between chronic residual arthralgias and cardiac involvement. Chronic arthralgias do not in themselves reflect active infection, nor do they lead to rheumatic heart disease.

COMMENT

The clinical material presented clearly indicates that intensive salicylate therapy instituted in the first twenty-five days of the acute illness in young adults successfully suppresses rheumatic infection. Acute articular and toxic manifestations are dramatically relieved. Significant cardiac residua are prevented if therapy is instituted before significant signs of carditis have appeared. Already existing carditis is favorably influenced. The period of active infection is materially shortened, and polycyclic recrudescences and residual chronic infection, although not prevented, occur less frequently in patients receiving intensive salicylate therapy than in those receiving symptomatic therapy.

Oral therapy is as effective in most instances as treatment administered by the intravenous route. Nevertheless, salicylates given intravenously are more effective in controlling severe and more refractory infections and are required in such cases. Fulminating infections do not always respond favorably. Thus, 1 patient with extensive rheumatic pneumonitis and another with acute pancarditis died shortly after treatment was begun. In 2 others receiving salicylates intravenously, resort to pericardial paracentesis for relief of effusion was not avoided. The preponderance of evidence, nevertheless, indicates that already existing significant carditis is favorably influenced.

The patients included in this study represent a group from whom persons with milder spontaneously subsiding infections have, for the most part, been excluded. If such persons are added, the 7.4 per cent incidence of significant cardiac residua in the intensively treated group would be even lower. Likewise, the effectiveness of intensive salicylate therapy, as reported in this study, applies only to those patients for

whom treatment was instituted within the first twenty-five days of the acute illness. Experience with patients with chronic rheumatic fever and with patients treated late in their illness has been far less favorable.

Chronic arthralgias, as an isolated symptom, do not reflect active rheumatic fever. No relationship was observed between chronic arthralgia and cardiac involvement, and those patients who exhibited residual arthralgias were remarkably free from heart disease. Therefore, the persistence of low grade arthralgias without other evidence of active infection does not dictate the restriction of physical activity as a prophylaxis against cardiac complications.

Accepting the value of Coburn's intensive salicylate regimen in cases of acute rheumatic fever, the problem of its safe yet effective application remains to be considered. These factors are discussed in a subsequent paper.⁶

CONCLUSIONS

1. Intensive salicylate therapy suppresses rheumatic infection in the acute stages occurring in young adults when treatment is instituted within twenty-five days after inception of the acute infection.
2. Acute articular and toxic manifestations are dramatically relieved.
3. Significant cardiac residua are prevented if therapy is instituted before signs of significant carditis have appeared. Already existing acute carditis is favorably influenced, although residual stigmas are not necessarily prevented.
4. The period of active infection is materially shortened, and relapses and residual chronic infection, although not prevented, occur less frequently in patients receiving intensive salicylate therapy than in those receiving symptomatic therapy.

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CHANGES IN HEMOGLOBIN AND TOTAL PLASMA PROTEIN AFTER INJECTION OF MERCUROPHYLLINE

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SINCE Saxl and Heilig¹ introduced the organic mercurial diuretics into the treatment of cardiac edema, many studies have been reported concerning their mechanism of action. The renal action of these diuretics has been proved by experiments on the isolated heart-lung-kidney preparation (Gremels²) and by observations on transplanted kidneys (Govaerts³). Investigations using the creatinine clearance method on dogs (Schmitz⁴) and on men (Herrmann and his colleague⁵) showed that the administration of these diuretics effected a diminished tubular reabsorption.

Evidence for an extrarenal action of the organic mercurial diuretics has also been brought forward, but is less convincing. The method usually employed when this problem of renal as against extrarenal action of mercurial diuretics is investigated is to examine the fluctuations in hemoglobin content or hematocrit values, total plasma protein and plasma volume during diuresis. It is reasoned that a primary extrarenal action of these drugs, effecting a transfer of tissue fluids to the blood stream, will result in a temporary hydremia, i. e., an increase in plasma volume, with a fall in hemoglobin and plasma protein. On the other hand, a preponderantly or exclusively renal action will cause hemoconcentration.

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1. Saxl, P., and Heilig, R.: Ueber die diuretische Wirkung von Novasurol und anderen Quecksilberinjektionen, *Wien. klin. Wchnschr.* **33**:943, 1920; Ueber die Novasuroidiurese, *Ztschr. f. d. ges. exper. Med.* **38**:94, 1923.

2. Gremels, H.: Zur Pharmakologie der Diurese, *Klin. Wchnschr.* **7**:1791, 1928.

3. Govaerts, P.: Origine renale ou tissulaire de la diurésé par un compose mercurial organique, *Compt. rend. Soc. de biol.* **99**:647, 1928.

4. Schmitz, H. L.: Studies on the Action of Diuretics: The Effect of Euphyllin and Salyrgan upon the Glomerular Filtration and Tubular Resorption, *J. Clin. Investigation* **11**:1075, 1932.

5. Herrmann, G., and Decherd, G. M., Jr.: Further Studies on the Mechanism of Diuresis with Special Reference to the Action of Some Newer Diuretics, *J. Lab. & Clin. Med.* **22**:767, 1937.

Contradictory findings (i. e., hemoconcentration and hemodilution) have been reported by different investigators, and these have been interpreted as arguments for either of the two theories of the site of action of the mercurial diuretics.

It was the purpose of the present investigation to study some factors which might explain the variability of the changes in the hemoglobin and total plasma protein due to the administration of the mercurial diuretics. It will be shown that, whereas the time at which the blood is examined after the injection of the mercurial diuretics is of minor importance, the presence or absence of peripheral edema is a decisive factor in determining the direction of the changes in hemoglobin and plasma protein during diuresis.

MATERIAL AND METHODS

Fluctuations in hemoglobin and total plasma protein were studied in 34 patients during the diuresis following injection of mercuraphylline. Of these patients 23 had congestive heart failure, 8 had cirrhosis of the liver in the state of decompensation and 2 had carcinomatosis of the peritoneum with ascites. The congestive heart failure was due to rheumatic heart disease in 14 cases, to hypertension and arteriosclerosis in 7 and to ephysema of the lungs in 2. Repeated mercuraphylline injections (two to four) were given to 13 patients and the resulting blood changes studied, so that altogether 57 experiments were performed.

In 29 instances the patients had peripheral edema at the time of the experiment. Twenty of these patients had heart failure, 8 cirrhosis of the liver and 1 carcinomatosis of the peritoneum. In the other 28 instances no peripheral edema was present at the time at which the mercurial diuretic was given the patients.

Six patients with heart failure were investigated at a time when they exhibited peripheral edema and again at a later date when it was absent.

Prior to the injection of mercuraphylline all patients were kept in bed for several days on restricted fluids and a diet low in salt. After two days of preparatory treatment with ammonium chloride (3 to 5 Gm. daily) mercuraphylline (1 to 2 cc.) was injected intravenously. The quantity of fluids allowed during the twenty-four hours following injection varied from 600 to 1,000 cc. The body weight was recorded immediately before and twenty-four hours after injection. The quantity of urine produced between the times of blood sampling was measured. Estimations of hemoglobin and plasma—or of serum protein—were made at the time of injection of the diuretic and repeated within each of the following periods: one to seven hours, seven to thirteen hours and seventeen and one-half to twenty-eight hours after injection. Blood

estimations within the one to seven hour period were performed in a limited number of cases only. All blood samples were taken before meals. They were obtained by venipuncture, without stasis. Hemolyzed blood was discarded.

In the cases designated by "K. H." (column "method" of table 1), the specific gravity of the serum was determined by the falling drop method of Kagan.⁶ The protein values were calculated from the specific gravity using the formula of Kagan.⁷ The blood hemoglobin content was determined using the method of Heilmeyer⁸: 0.2 cc. of oxalated blood was diluted with 9.8 cc. of 0.4 per cent solution of ammonia, and a knife point of sodium thiosulfate was added. Colorimetric readings were taken with the Pulfrich *Stufen* photometer. If duplicate values differing by more than 3 per cent were obtained, additional determinations on the same blood sample were made. The extinction factor used was 0.92.⁸

In the cases marked with "C" (table 1, column "method"), the cupric sulfate method of Phillips and his colleagues⁹ was used to determine the specific gravity of whole blood and plasma. The set of cupric sulfate solutions differing in specific gravity by 0.0001 was employed. Hemoglobin and plasma protein values were calculated according to the nomograph given by the authors.

RESULTS

The results of the observations are arranged in tables 1 and 2. In table 1 the cases in which there was edema are recorded. In table 2 the cases in which there was not edema are recorded.

The changes observed one to seven hours after injection of the diuretic ranged for hemoglobin from — 8.5 per cent to + 19.5 per cent and for total plasma protein from — 4.1 per cent to + 25.1 per cent.

6. Kagan, B. M.: A Simple Method for the Estimation of Total Protein Content of Plasma and Serum: I. A Falling Drop Method for the Determination of Specific Gravity, *J. Clin. Investigation* **17**:369, 1938. de Vries, A.: Determination of Serum Protein: An Account of Kagan's "Falling Drop" Method with Certain Modifications, *Acta med. orient.* **3**:53-57, 1944.

7. Kagan, B. M.: A Simple Method for the Estimation of Total Protein Content of Plasma and Serum: II. The Estimation of Total Protein Content of Human Plasma, and Serum by the Use of the Falling Drop Method, *J. Clin. Investigation* **17**:373, 1938.

8. Heilmeyer, cited by Zeiss, C., and Krebs, W.: *Klinische Kolorimetrie mit dem Pulfrich-Photometer*, Leipzig, 1935.

9. Phillips, R. A.; Van Slyke, D. D.; Dole, V. P.; Emerson, K., Jr.; Hamilton, P. B., and Archibald, R. M.: Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma, report from United States Naval Research Unit at the Hospital of the Rockefeller Institute for Medical Research.

TABLE 1.—Instances in Which Patients Had Peripheral Edema

Number	Initials	Failure of Left Side of Heart	Enlargement of Periph-eral Liver	Mercurio-phyl-lides	At the Time of Injection		Within 1-7 Hours After Injection			Within 7-13 Hours After Injection			Within 17½-28¾ Hours After Injection			Loss of Wt. Kg.
					Hemo-globin Gm. per 100 Cc.	Protein Gm. per 100 Cc.	Percentage Change*	Hemo-globin	Protein	Total Cc.	Diuresis Cc. Min.	Percentage Change*	Hemo-globin	Protein	Total Cc.	
1	B. Ts	..	+	+	11.3	0.44	4.15	8.5	8	1.4
2	E. S.	..	+	+	13.3	7.0	11	0.4
3	E. S.	..	+	+	11.8	6.2	8	0.2
4	E. S.	..	+	+	12.6	6.55	10	1.9
5	E. S.	..	+	+	12.4	6.0	9	1.2
6	G. A.	..	+	+	14.75	4.98	8.35	2.3
7	G. A.	..	+	+	12.0	4.69	7.30	5.5
8	Sh. B.	..	+	+	4.0	1	+ 8.5	7.30	+ 16.5
Diagnosis: Heart Failure; Rheumatic Heart Disease																
9	A. O.	+	+	+	14.7	7.2	11	3.0
10	A. O.	+	+	+	14.2	6.6	10	2
11	B. G.	+	+	+	14.15	5.78	5.15	0	1,300	4.13	10	2.4
12	B. G.	+	+	+	13.8	5.83	5	+ 2.5	+ 6.7	1,925	6.42	11.30	+ 2.5	+ 5.5	2,990	3.4
13	F. Seh.	+	+	+	13.55	5.92	5	- 1	+ 7.8	1,440	4.80	9	+ 6.3	+ 17.4	3,000	1.4
14	F. B.†	+	+	+	10.05	6.53	10	- 2.5	- 6.1	850	...
15	A. Ch.	+	+	+	6.69	3.45	+ 3.4	9.45	+ 4.8	3.0
16	J. M.	+	+	+	6.13	6	+ 0	6	2.9
17	J. M.	+	+	+	5.82	1	- 2.4	9	+ 3.4	1.3
Diagnosis: Hypertensive Arteriosclerotic Heart Disease																
18	N. B. O.	+	+	+	15.7	6.8	8	- 8.3	- 3	1,300	2.3
19	N. B. O.	+	+	+	16.3	7.3	12	- 2	0	1,220	2.5
20	N. B. O.	+	+	+	14.9	7.42	9	+ 9.4	+ 2.4	1,350	2.5
21	Sh. M.	+	+	+	13.7	5.94
22	D. S.	+	+	+	16.6	6.78	6.30	0	- 1.5	2,280	5.9	13	- 1.5	+ 3.8	3,060	...
23	E. F.	+	+	+	11.95	5.3	5	0	0	270	0.9	10	- 2.7	0	610	0.7
24	J. F.	+	+	+	15.55	5.85	5.30	- 1	- 1.5	1,060	3.21	8.30	0	0	1,610	2.2
25	J. K.	+	+	+	10.65	6.02	2.30	- 2.8	- 4.1	8	0	0	1,065	3.5
26	J. K.	+	+	+	11.3	5.96	7	0	+ 6.9	1.9
Diagnosis: Corpulmonale																
27	A. Sh.	±	+	+	18.5	6.2	7.25	+ 10	- 9.2	1.1
28	A. G.	±	+	+	17.35	5.26	7	+ 3.4
Diagnosis: Carcinomatosis of the Peritoneum																
29	J. B.	..	+	+	10.05	6.43	9	+ 6.5	+ 5.9	1,450	2.8

* The changes in hemoglobin and in plasma protein are expressed in percentages of the amounts found at the time of the injection of the diuretic. + Indicates a rise and - indicates a fall in amount of hemoglobin or plasma protein.

† The numbers in parentheses refer to experiments on the same patient in table 2.

‡ Subacute bacterial endocarditis.

TABLE 2.—Instances in Which Patients Were Without Peripheral Edema

Number	Initials	Failure of Left Side of Heart	Enlargement of Liver	Mercurio-phyline	Aspirin	At the Time of Injection		Within 1-7 Hours After Injection			Within 7-13 Hours After Injection			Within 17½-28½ Hours After Injection			Loss of Wt. Kg.		
						Hemo-globin per 100 Cc.	Protein per 100 Cc.	Percentage Change*	Hemo-globin	Protein	Total Cc.	Diuresis Cc. Min.	After Hours	Hemo-globin	Protein	Total Cc.		Diuresis Cc. Min.	
Diagnosis: Cirrhosis of the Liver																			
30	A. R.	..	—	2	K. H.	14.15	5.43	5	+ 6.7	+ 7.7	21	+ 3.1	4,000	3.18	3.4
31	A. E.	..	—	2	K. H.	14.45	4.98	6	+ 4.1	+ 9.8	250	0.7	24	+11.8	+15.1	4,135	2.87	3.7
32	A. R.	..	—	1	O.	15.1	5.32	9.30	24	+ 3.3	+ 0.8	1,650	1.12	1
33	B. M.	..	—	2	O.	12	6.68	11	24	+ 8.8	+ 8.1	2,950	2.09	2.1
34	F. P.	..	—	2	O.	12.30	5.44	9.15	2.4
35	B. J. E.	..	—	2	K. H.	15.4	5.18	9	0	+ 3.3	2,600	1.84	...
Diagnosis: Heart Failure; Rheumatic Heart Disease																			
36	R. A.	+	+	1.5	O.	11.95	7.2	12.30	22.30	2,140	1.59	1.4
37	R. A.	+	+	1.5	O.	12	7.4	11.30	24	+ 6.7	+13.5	2,350	1.63	1.7
38	R. A.	+	+	2	O.	12.2	6.85	10	24	+13.1	+21.9	3,080	2.14	2.7
39	O. O.	+	+	2	O.	15.7	6.2	10	24	+10.2	+ 9.7	2,000	1.39	1.5
40	Ch. W.	+	+	2	K. H.	10	6.05	5.30	+19.5	+25.1	1,550	4.69	10	24	+22.0	+20	4,550	3.16	4.9
41	Ch. W.	+	+	2	K. H.	13.05	7.40	4	— 1.1	— 1	1,025	4.27	9	23.30	+ 5.7	+ 7.8	2,175	1.54	2.3
42	Ch. W.	+	+	2	K. H.	9.6	6.33	11.30	24	+ 2.5	— 2	1,330	0.94	0.6
43	M. P.	+	+	2	K. H.	16.95	6.87	12	24	+ 0.6	+ 1.5	1,340	0.93	...
44	B. G.	+	+	2	K. H.	13.2	6.35	4.15	+ 3.8	1,470	5.18	11	23.30	+ 7.2	— 1.5	2,785	1.07	2.3
(11-12)†																			
45	A. Ch.	+	+	2	O.	14.3	7.03	4.30	+ 8.4	+ 5.5	480	1.77	9.15	23.30	+11.2	+ 5.5	950	0.70	0.3
46	S. G.	+	+	1.5	O.	11.85	6.71	2	— 2	+ 3.9	8	24	+14.3	+20.6	3,450	2.19	2.5
47	J. B.	+	+	2	K. H.	16.2	6.63	0	+ 3.4	340	2.83	7.30	25	+ 6.8	+10.8	2,060	1.37	1.6
48	M. K.	+	+	2	K. H.	16.05	6.27	3	+ 1.9	480	2.66	7.30	21	+ 9.6	+15.3	2,500	1.98	1.6
49	F. Seh.	+	+	2	K. H.	13.2	6.60	2	+ 3.7	+ 3.8	455	3.79	7.30	24	0	+10.6	2,245	1.56	2.5
(13)																			
50	A. C.	+	+	1.5	K. H.	6.17	17.30	+22.7	3,800	3.62	3.4
(9-10)																			
51	A. C.	+	+	1.5	K. H.	6.81	21.30	+12.9	3,000	2.33	3.7
Diagnosis: Hypertensive Arteriosclerotic Heart Disease																			
52	N. B. C.	+	+	2	O.	14.7	7.78	10	24	+ 4.8	+ 1.3	1,970	1.37	2.5
(8-10-20)																			
53	E. F.	+	+	2	O.	11.65	6.75	9.30	24	+ 3.0	+ 7.7	1,170	0.81	0.6
(23)																			
54	J. F.	+	+	1.5	K. H.	15.4	6.10	5.15	0	+ 2.5	1,520	4.82	9.15	23.15	+10.2	+10.8	5,530	3.97	4.0
(24)																			
55	M. P.	+	+	1.5	K. H.	17.8	6.77	3	0	+ 2.3	500	2.77	7.30	21	+ 6.7	+ 8	1,790	1.42	...
Diagnosis: Carcinomatosis of the Peritoneum																			
56	W. R.	—	—	2	K. H.	5.73	1	+ 1.5	8.45
Diagnosis: Normal																			
57	J. M.	—	—	2	K. H.	6.22	4.30	+12	1,420	5.26	8.30

* The changes in hemoglobin and in plasma protein are expressed in percentages of the amounts found at the time of the injection of the diuretic. + indicates a rise and — indicates a fall in amount of hemoglobin or plasma protein.

† The numbers in parentheses refer to experiments on the same patient in table 1.

The changes observed seven to thirteen hours after injection of the diuretic varied for hemoglobin from -10.5 to $+18$ per cent and for total protein from -9.2 per cent to $+21.1$ per cent.

The changes observed seventeen and one-half to twenty-eight hours after injection ranged for hemoglobin from -5.3 per cent to $+22$ per cent and for total protein from -9.7 per cent to $+22.7$ per cent.

TABLE 3.—Correlations in Changes in Hemoglobin and/or Serum Protein After Injection of Diuretic

Correlation in Individual Cases Between		Coeff- cient of Correla- tion (%)*	Standard Error of This. Coeff- cient (%)	Average of Changes in Percentage †	M_x	Average of Changes in Percentage †	M_y	No. of Cases "
(x) Changes in	(y) Changes in							
Patients With Edema								
A. Hemoglobin after 7-13 hours	Protein after 7-13 hours	80.41	± 5.33	Hemoglobin after 7-13 hours	+2.60	Protein after 7-13 hours	+4.57	44
B. Hemoglobin after 24 hours	Protein after 24 hours	65.25	± 8.67	Hemoglobin after 24 hours	+4.32	Protein after 24 hours	+3.46	44
C. Hemoglobin after 7-13 hours	Hemoglobin after 24 hours	59.46	± 9.86	Hemoglobin after 7-13 hours	+2.28	Hemoglobin after 24 hours	+3.47	43
D. Protein after 7-13 hours	Protein after 24 hours	73.24	± 7.15	Protein after 7-13 hours	+3.99	Protein after 24 hours	+4.35	42
Patients Without Edema								
E. Diuresis in 24 hours: Cc. minute	Hemoglobin after 24 hours	59.71	± 14.04	Average of diuresis in Cc. minute	1.76	Hemoglobin after 24 hours	+7.55	21
F. Diuresis in 24 hours: Cc. minute	Protein after 24 hours	52.97	± 14.70	Average of diuresis in Cc. minute	1.92	Protein after 24 hours	+9.48	24

$$\text{* Coefficient of correlation: } r = \frac{\sum (x \cdot y) - n \cdot \underline{M}_x \cdot \underline{M}_y}{\sqrt{[\sum (x^2) - n \cdot \underline{M}_x^2] [\sum (y^2) - n \cdot \underline{M}_y^2]}}$$

$$\text{Standard error of coefficient of correlation: } \frac{1 - r^2}{\sqrt{n}}$$

$$(n : \text{number of cases; } \underline{M} : \text{average} = \frac{\text{Total}}{n})$$

A correlation is considered significant when the coefficient of correlation amounts to three times or more its standard error.

† The changes in hemoglobin and in plasma protein are expressed in percentages of the amounts found at the time of injection of the diuretic. + indicates a rise and - a fall in amount of hemoglobin or plasma protein.

Statistical calculations of the results of the observations are given in tables 3 and 4 and lead to the following conclusions.

1. The figures obtained by simultaneous examinations of hemoglobin and total protein seven to thirteen hours after injection of the diuretic show that the changes in hemoglobin and total protein are

highly correlated; i. e., they change in the same direction (table 3, A). The same holds true for changes in hemoglobin and total protein found after approximately twenty-four hours (table 3, B).

TABLE 4.—*Effect of Edema on Difference in Changes in Hemoglobin and Plasma Protein After Injection of Diuretic*

	Patients with Edema				Patients Without Edema				Difference of Values for Patients With Edema and Patients Without		
	No. of Patients	Average of Change (%)	Standard Deviation	Standard Error of the Average	No. of Patients	Average of Change (%)	Standard Deviation	Standard Error of the Average	Difference Between the Two Averages	Standard Error of This Difference	Critical Ratio
Changes in	n_x	M_x^*	σ_x^\dagger	e_x^\ddagger	n_y	M_y^*	σ_y^\dagger	e_y^\ddagger	$M_x - M_y$		
G. Hemoglobin after 7-13 hours	23	-0.839	4.435	± 0.925	23	+5.926	5.303	± 1.107	6.765	1.442	4.691
H. Hemoglobin after 24 hours	24	-0.388	3.795	± 0.776	21	+7.550	5.234	± 1.142	7.938	1.381	5.749
I. Protein after 7-13 hours	27	+0.400	6.472	± 1.245	24	+8.800	7.648	± 1.561	8.400	1.997	4.207
J. Protein after 24 hours	24	+0.204	4.388	± 0.896	24	+9.479	7.143	± 1.458	9.275	1.711	5.420
K. Diuresis in 24 hours: Cc. minute	28	1.869	0.853	± 0.161	25	1.908	0.858	± 0.172	0.039	0.236	0.166

* The changes in hemoglobin and in plasma protein are expressed in percentages of the amounts found at the time of the injection of the diuretic. + indicates a rise and - a fall in amount of hemoglobin or plasma protein.

$$\dagger \text{ Standard deviation: } \sigma = \sqrt{\frac{\sum (x^2)}{n} - \left(\frac{\sum x}{n}\right)^2}$$

$$\ddagger \text{ Standard error of average: } e = \frac{\sigma}{\sqrt{n}}$$

$$\S \text{ Standard error of the difference between the two averages: } \sqrt{e_x^2 + e_y^2}$$

$$\parallel \text{ Critical ratio: } \frac{M_y - M_x}{\sqrt{e_x^2 + e_y^2}}$$

The average of change (M) does not differ significantly from 0, if 0 is in the range of $M \pm e$. The average of change does differ significantly from 0 if 0 does not fall in the range of $M \pm 3e$. The difference between the two averages is significant if the critical ratio is more than 3.

2. There is a significant correlation between the changes in hemoglobin found seven to thirteen hours and approximately twenty-four hours after the injection of the diuretic in individual cases (table 3, C).

The same holds true for the changes in protein found seven to thirteen hours and twenty-four hours after injection in individual cases (table 3, D).

The results of estimations of hemoglobin and total plasma protein performed one to seven hours after the injection are not analyzed statistically, as they are small in number. It seems that the changes are in the same direction as those occurring later after the injection.

3. The results of the calculations in tables 3 and 4 also indicate that the trend of changes in hemoglobin and plasma protein is quite different in the cases in which there is edema from the trend in cases in which there is not. In the cases in which there is edema the average changes of hemoglobin and total protein observed seven to thirteen hours, as well as twenty-four hours, after injection of the diuretic do not differ significantly from 0. On the other hand, in the cases in which there is not edema there is a significant rise in the average hemoglobin and total protein observed seven to thirteen hours, as well as twenty-four hours, after injection. The differences between the two groups of cases are statistically significant (table 4, G, H, I and J).

4. It may be expected that the changes in the hemoglobin and in the total protein will be dependent on the amount of urine and the rapidity of its production. If the renal action of mercuraphylline is accepted, then the more rapid the loss of water from the blood stream, the greater the hemoconcentration, as tissue fluids may not restore the blood volume fast enough. On the other hand, assuming the primary extrarenal action of the mercurial diuretics, a rapid diuresis would lessen the tendency to hemodilution. Therefore, as the observations on the patients could not be made at exactly the same time after the injection of the diuretic, the diuresis in different patients was expressed by the quantity of urine produced per unit of time (cubic centimeters per minute). The average rate of diuresis, calculated from the quantity of urine produced in twenty-four hours, amounted in the 28 cases in which there was edema to 1.689 cc. per minute, whereas in the 25 cases in which there was not edema the average rate was 1.908 cc. per minute (table 4, K). It therefore would appear that the contrast in blood changes between the two groups, the group in which there was edema and the group in which there was not, cannot be ascribed to any difference in rate of diuresis.

5. Statistical analysis finally shows that there is a positive correlation between the rate of diuresis and the hemoconcentration in the group in which there was not edema; the higher the rate of diuresis, the higher the rise in the two blood constituents (table 3, E and F). Such a correlation could not be established for the cases in which there was edema.

The observations on the changes in hemoglobin and total plasma protein occurring after repeated administrations of mercuraphylline to the same patient, in the presence or absence of edema, substantiate the principles which have been stated and will be described later.

PATIENT J. F. (clinical diagnosis: heart failure due to arteriosclerotic heart disease and hypertensive cardiovascular disease).—Experiment 24 was performed while edema was present (body weight 67.5 Kg.). The injection of mercuraphylline was followed by a urinary output of 1,880 cc. in twenty-four and one-half hours, but practically no change in hemoglobin or plasma protein was discerned during this period. In experiment 54 an injection of mercuraphylline was given to the same patient when edema was absent, though hepatic engorgement was still present (body weight 62 Kg.). On this occasion considerable hemoconcentration occurred. The urinary output, however, amounted to 5,530 cc. in twenty-three and one-fourth hours. This larger diuresis or the absence of edema or both may have been responsible for the hemoconcentration encountered in the second experiment.

PATIENT E. F. (clinical diagnosis: heart failure due to arteriosclerotic heart disease and hypertensive cardiovascular disease).—In the first experiment (no. 23) edema was present (body weight 53.2 Kg.). After the injection of mercuraphylline a urinary output of 1,410 cc. occurred in twenty-four hours. No significant changes in the blood were observed during this period. In the second experiment (no. 53) edema was absent (body weight 50.2 Kg.). An output of 1,170 cc. in twenty-four hours occurred after injection of mercuraphylline, and during the same period hemoconcentration was observed. In this case only the factor of edema can be held responsible for the difference in findings.

PATIENT B. G. (clinical diagnosis: heart failure due to rheumatic heart disease).—Mercuraphylline injected while edema was present (experiment 11, body weight 49 Kg.) produced a urinary output of 2,410 cc. in twenty-three hours, associated with hemodilution. A second injection (experiment 12), given when edema was slight (body weight 45.7 Kg.), produced urinary output of 3,670 cc. in twenty-three and one half hours, and on this occasion a slight hemoconcentration was observed. After a third injection (experiment 44) in the absence of edema (body weight 43.6 Kg.) urinary output of 2,785 cc. in twenty-three and one-half hours was associated with considerable hemoconcentration. The difference in blood changes found in the first and second experiments may be partially explained by the greater diuresis which occurred in the latter. However, the quantities of urine produced during the first and the third experiment were practically the same; here only the presence or absence of edema seemed to be responsible for the difference in the changes of the blood constituents.

PATIENT F. SCH. (clinical diagnosis: heart failure due to rheumatic heart disease).—When the first experiment was performed (no. 13), edema was present (body weight 65.1 Kg.), and after the injection of mercuraphylline, which was followed by excretion of 5,460 cc. of urine in twenty-three hours, hemoconcentration was observed. In the second experiment (no. 49) edema was absent, but the liver was still engorged (body weight 59.1 Kg.). On this occasion, after the injection of mercuraphylline a much smaller excretion of urine was observed (2,245 cc. in twenty-four hours), but hemoconcentration of practically the same degree as in the first experiment took place. In the first experiment the diuresis was so extensive that the hemoconcentration could not be compensated sufficiently by the inter-

stitial fluid, but the inflow of edema fluid prevented a rise in the blood constituents to a level higher than that observed in the second experiment, in which the output of urine was much smaller.

PATIENT N. B. C. (clinical diagnosis: heart failure due to arteriosclerotic heart disease).—The first injection (no. 18, on Oct. 19, 1944) was given while marked edema was present; inconsistent changes were observed during diuresis

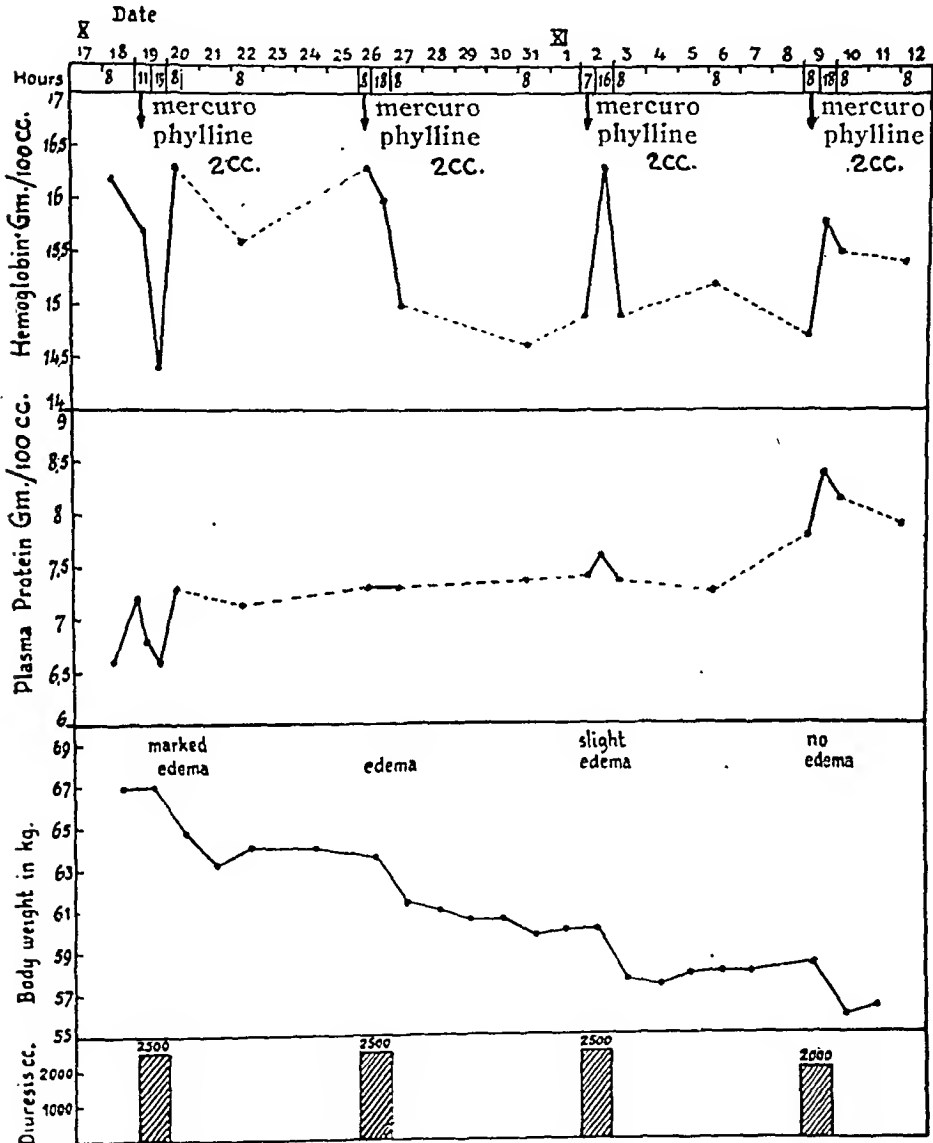


Fig. 1.—Changes in amount of hemoglobin and of plasma protein, extent of diuresis and degree of edema in patient N. B. C.

(first hemodilution, then concentration). At the time of the second injection (no. 19, on Oct. 26, 1944) edema was still present; a fall in hemoglobin was observed, but the protein level did not change. In the third experiment (no. 20, on Nov. 2, 1944) edema was slight, and a temporary rise of hemoglobin occurred. At the time of the fourth injection (no. 52, on Nov. 9, 1944) edema was absent, and a sustained rise of hemoglobin and protein was found during

diuresis. Thus with the disappearance of edema an increasing hemoconcentration took place. As the quantities of urine produced in all four experiments were practically the same, the influence of edema on the fluctuations of the amounts of hemoglobin and plasma protein is clearly demonstrated in this case.

PATIENT A. C. (clinical diagnosis: heart failure due to rheumatic heart disease).—The patient was admitted twice. During the first period of hospitalization the effect of two injections was studied (no. 50, on Aug. 15, 1943, and no. 51 on Aug. 22, 1943), edema being absent in both experiments. A sharp rise in protein occurred. A year later the patient was readmitted. Two injec-

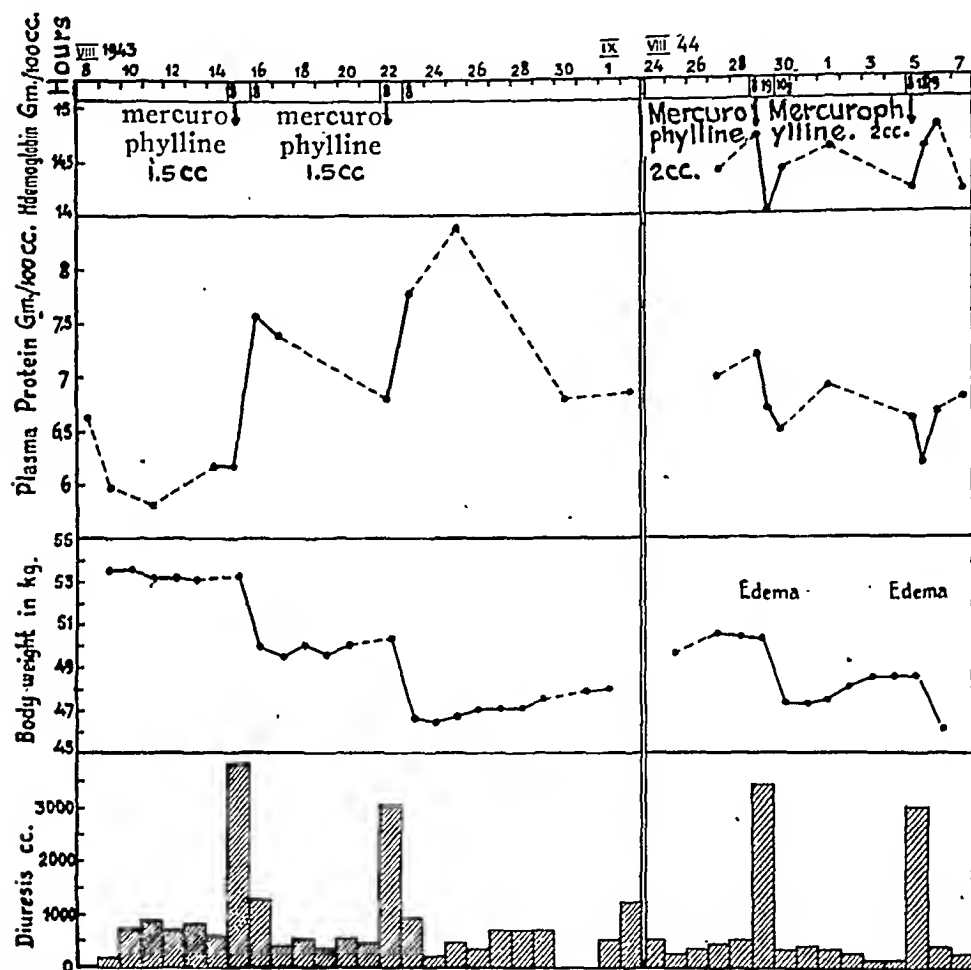


Fig. 2.—Changes in amount of hemoglobin and of plasma protein, extent of diuresis and degree of edema in patient A. C.

tions of mercurio-phylline were given (no. 9, on Aug. 29, 1944, and no. 10, on Sept. 5, 1944), edema being manifest on both occasions, and inconsistent small changes in the blood were observed. As the output of urine was practically the same in all four experiments, the influence of edema on the results obtained seems to be well illustrated in this case also.

PATIENT CH. W. (clinical diagnosis: heart failure due to rheumatic heart disease).—In this case three injections of mercurio-phylline were given (no. 40, 41 and 42), edema being absent on all three occasions. The changes in hemoglobin and plasma protein found during diuresis illustrate the influence of the

quantity of urine produced on the degree of hemoconcentration. The larger the diuresis the more pronounced the hemoconcentration.

COMMENT

Observations on fluctuations of hematocrit readings and values for hemoglobin and total plasma protein during the diuresis caused by parenteral administration of mercurial preparations have been made by various observers at different times following the injection of the drug. Differences in the time of examination of the blood may be partly responsible for the contradictory results obtained, this point having also been made by Lyons and his colleagues.¹⁰

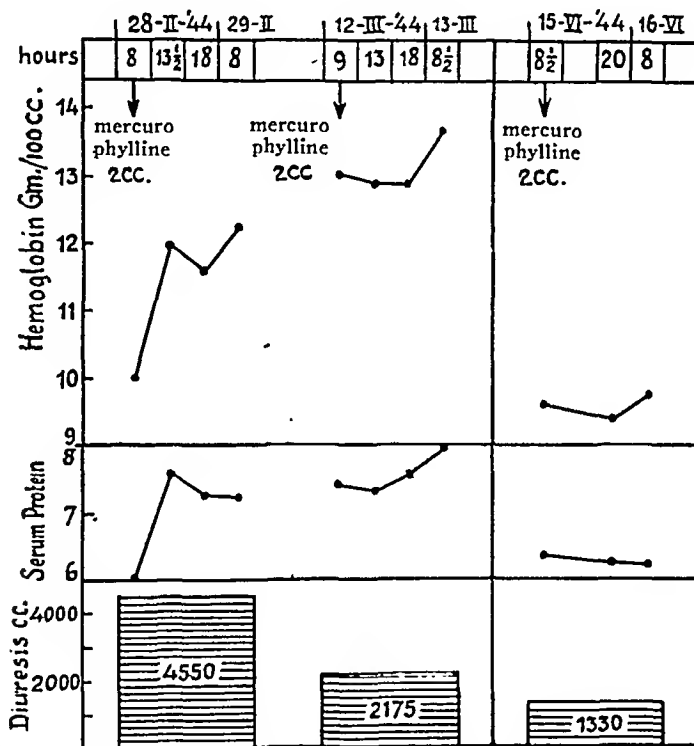


Fig. 3.—Changes in amount of hemoglobin and of serum protein and extent of diuresis in patient Ch. W.

Some investigators observed hemodilution during a short period after injection of the drug, followed by hemoconcentration later.¹¹

10. Lyons, R. H.; Avery, N. L., and Jacobson, S. D.: Effect of Dehydration Produced by Mercupurin on the Plasma Volume of Normal Persons, *Am. Heart J.* **28**:247, 1944.

11. (a) Claussen, F.: Ueber die Diurese des Herzkranken, *Ergebn. d. inn. Med. u. Kinderh.* **43**:764, 1932; cited by Bryan and others.²⁰ (b) Meyer, P.: Untersuchungen über den kolloidosmotischen Druck des Blutes: I. Oedem und Oedemausschwemmung, *Ztschr. f. klin. Med.* **115**:647, 1931; (c) Untersuchungen

However, close analysis of the reports on this subject shows that there are inconsistencies even in results obtained over the same time intervals.

During the first four hours after injection of the diuretic a decrease in plasma protein was observed by several investigators.¹² Others noted an increase.¹³ Inconsistent changes were observed by Swigert and Fitz.¹⁴ The hematocrit value was found to be increased¹⁵ or variable.¹⁶ Some authors found a decrease in plasma volume.¹⁷ Feher,^{16a} on the other hand, reported an increase, and inconsistent findings were obtained by Swigert and Fitz.¹⁴

Numerous studies performed three to twenty-four hours after the injection of the diuretic revealed an increase in plasma protein¹⁸ and

über den kolloidosmotischen Druck des Blutes: II. Die Salyrgandiurese, *ibid.* **116**:174, 1931. (d) Serby, A. M.: The Pharmacology and Therapeutics of Novasurol, *Arch. Int. Med.* **38**:374 (Sept.) 1926. (e) Crawford, J. H., and McIntosh, J. F.: Use of Novasurol in Cardiac Edema, *J. Clin. Investigation* **1**:333, 1925; cited by Bryan and others.²⁰ (f) Kylin, E.: Studien über den kolloidosmotischen (onkotischen) Druck: Ueber die Einwirkung verschiedener Diuretika auf den kolloidosmotischen Druck, *Arch. f. exper. Path. u. Pharmacol.* **164**:33, 1932.

12. Bohn, H.: Experimentelle Studien über die diuretische Wirkung des Novasurols, *Ztschr. f. d. ges. exper. Med.* **31**:303, 1923; Fortgesetzte Studien über Novasural, seine Wirkung bei verschiedenen Lebensaltern und bei Diabetikern, sowie sein etwaiger Einfluss auf Ionenverschiebungen im Organismus, *Deutsches Arch. f. klin. Med.* **143**:225, 1923; cited by Lyons and others.¹⁰ Saxl and Heilig.¹ Footnote.¹¹

13. (a) Calvin, D. B.; Decherd, G. M., and Herrmann, G.: Plasma Protein Shifts During Diuresis, *Proc. Soc. Exper. Biol. & Med.* **44**:578, 1940. (b) Nonnenbruch, W.: Ueber die Wirkung des Novasurols auf Blut und Diurese, *München med. Wchnschr.* **68**:1282, 1921. (c) Schmitz, H. L.: Studies on the Action of Diuretics: The Effect of Salyrgan upon the Water Content of the Plasma as Measured by the Refractive Index, *J. Clin. Investigation* **12**:741, 1933; cited by Bryan and others.²⁰ (d) Bryan, A. H.; Evans, W. A., Jr.; Fulton, M. N., and Stead, E. A., Jr.: Diuresis Following the Administration of Salyrgan: Its Effect on Specific Gravity, the Total Nitrogen and the Colloid Osmotic Pressure of the Plasma of Normal and of Edematous Dogs, *Arch. Int. Med.* **55**:735 (May) 1935.

14. Swigert, V. W., and Fitz, R.: The Effect of Mersalyl (Salyrgan) on the Plasma Volume, *J. A. M. A.* **115**:1786 (Nov. 23) 1940.

15. Evans, W. A., Jr., and Gibson, J. G.: The Blood Volume in Diuresis, *Am. J. Physiol.* **118**:251, 1937.

16. (a) Feher, S.: Salygrandiurese und zirkulierende Blutmenge, *Wien. klin. Wchnschr.* **42**:964, 1929. (b) Swigert and Fitz.¹⁴

17. (a) Calvin, D. B.; Decherd, G. M., and Herrmann, G.: Response of Plasma Volume to Diuretics, *Proc. Soc. Exper. Biol. & Med.* **44**:529, 1940; (b) Calvin and others.^{13a} Evans, and Gibson.¹⁵

18. (a) Lopes Cardozo, E.: Invloed van Salyrgan op het Bloedvolume, *Nederl. tijdschr. v. geneesk.* **83**:5528, 1939. (b) Borst, J. O. G.: Behandeling van Decompensatio Cordis door uitdrijving van keukenzout, *ibid.* **81**:5664, 1937. (c) Lyons, Avery and Jacobson.¹⁰ Footnote 11. Footnote 13 a, c and d. Calvin, Decherd and Herrmann.^{17a}

hematocrit value.¹⁹ Some authors, however, found inconsistent changes in hematocrit value²⁰ and plasma protein¹⁴ at this period of examination. A decrease in plasma volume was reported by some investigators,²¹ while others obtained inconsistent results.²² Thus the time factor alone does not explain satisfactorily the contradictory observations reported in the literature.

My observations on the changes in the total protein and the hemoglobin content of the blood occurring during the period of one to seven hours after injection of mercurphylline reveal that the fluctuations of these blood constituents are generally in the same direction as those occurring at later hours. The statistical analysis of my results leads to the conclusion that within a period of seven to approximately twenty-four hours after the injection the average figure obtained for changes in hemoglobin and protein is independent of the time of examination.

Differences in the type of case in which diuresis studies have been made might also be a factor responsible for the inconsistent results reported by previous observers.¹⁹ However, there were irregular findings concerning changes in hemoglobin and plasma protein during diuresis in the same disease, for instance in heart failure,²³ in cirrhosis of the liver^{11c} and in hypoproteinemia.^{13d} My results also show that the underlying disease has no influence on the changes in the blood occurring during diuresis.

Analysis of my material indicates that the direction of changes in hemoglobin and plasma protein occurring during diuresis after injection of mercurphylline depends on the presence or absence of peripheral edema. In cases in which there is not edema a significant hemoconcentration generally takes place, which is the more pronounced the greater the amount of urine produced in a given time. On the other hand, in cases in which there is edema the levels of hemoglobin and total plasma protein usually remain the same.

Some observations reported previously are consistent with my observations. Lyons and his colleagues¹⁹ consistently found hemoconcentration in normal persons during diuresis after the administration of mercurphylline. Swigert and Fitz¹⁴ and Goldhammer and his col-

19. Lyons, Avery and Jacobson.¹⁰ Borst.^{18b}

20. (a) Goldhammer, S.; Leiner, G., and Schierf, D.: Ueber die zirkulierende Blutmenge vor und nach der Quecksilberdiurese, *Klin. Wchnschr.* **14**:1109, 1935.
(b) Swigert and Fitz.¹⁴ Lopez Cardoso,^{18a}

21. Lyons, Avery and Jacobson.¹⁰ Calvin, Decherd and Herrmann (footnotes 13a and 17a). Lopes Cardoso.^{18a}

22. Brown, G. E., and Rowntree, L. G.: The Volume and Composition of the Blood, and the Changes Incident to Diuresis, in Cases of Edema, *Arch. Int. Med.* **35**:129 (Jan.) 1925. Swigert and Fitz.¹⁴ Goldhammer, Leiner and Schierf.^{20a}

23. Crawford and McIntosh.^{11c} Swigert and Fitz.¹⁴

leagues^{20a} described cases in which there was edema in which the changes in hemoglobin and total plasma protein were slight or absent. However, Evans and Gibson¹⁵ and Bryan and his colleagues^{18d} found hemoconcentration during diuresis in the presence of edema. Hemoconcentration also occurred in a few of my cases in which there was edema. It may be that other factors were predominant in the cases; nevertheless, such exceptions do not minimize the value of the general conclusions drawn from the statistical analysis of a large number of cases.

The conclusions drawn from my statistical calculations are consistent with the theory of the renal action of mercurial diuretics (though it does not explain the finding of hemodilution in a few of my cases).²⁴ Although the changes in hematocrit value or amounts of hemoglobin and total plasma protein cannot be considered a quantitative index of fluctuations in plasma volume,²⁵ it is assumed that they do indicate the direction of its change.¹⁰

A primary renal action of the diuretic will cause a diminution in the plasma volume with hemoconcentration. This effect will be counteracted by an inflow of interstitial fluid into the blood stream. Hemoconcentration will be slight or absent if the restoration of the plasma volume occurs quickly and adequately. This will be the case if large amounts of interstitial fluid are available. That an increase in interstitial fluid actually effects an increase in plasma volume was demonstrated by Warren and Stead.²⁶

It follows that in the absence of edema hemoconcentration will take place and that it will be more pronounced when diuresis is extensive. The interstitial fluid accumulated in cases in which there is pulmonary

24. Mercupurin contains theophylline. According to Calvin and his colleagues,^{17a} blood volume may be increased by the action of xanthine preparations, but as this effect passes off within six hours it has no influence on the changes observed seven to twenty-eight hours after injection.

25. Stead, E. A., Jr., and Ebert, R. V.: Relationship of the Plasma Volume and the Cell Plasma Ratio to the Total Red Cell Volume, *Am. J. Physiol.* **132**: 411, 1941. Ebert, R. V., and Stead, E. A., Jr.: Demonstration That the Cell Plasma Ratio of Blood Contained in Minute Vessels Is Lower Than That of Venous Blood, *J. Clin. Investigation* **20**:317, 1941. Kety, S. S., and Pope, A.: Cardiovascular System in Traumatic Shock, *Am. Heart J.* **27**:601, 1944. Beattie, J.: Fate of Transfused Plasma, *Lancet* **2**:445, 1942. Ebert, R. V.; Stead, E. A., Jr.; Warren, J. W., and Watts, W. E.: Plasma Protein Replacement After Hemorrhage in Dogs With and Without Shock, *Am. J. Physiol.* **136**:299, 1942. Hahn, P. F., and others: Red Cell and Plasma Volumes (Circulating and Total) as Determined by Radio Iron and by Dye, *J. Exper. Med.* **75**:221, 1942.

26. Warren, J. V.; Merrill, A. J., and Stead, E. A., Jr.: Role of Extracellular Fluid in Maintenance of Normal Plasma Volume; *J. Clin. Investigation* **22**:635, 1943. Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure, *Arch. Int. Med.* **73**:138 (Feb.) 1944.

congestion and hepatic engorgement but no peripheral edema seems unable of itself to restore the plasma volume rapidly enough after the loss of fluid through the kidney.

For a given loss of water from the blood stream the percentage change in plasma protein ought to be much larger than that in hemoglobin, as the percentage of plasma protein is related to the plasma volume while the percentage of hemoglobin is related to the total blood volume. In many instances this was actually observed (e. g., injections 47 and 48), but in others the rise in protein was the same as, or even less than, that in hemoglobin (e. g., experiments 40 and 45). In the latter case plasma protein supposedly leaves the blood stream during the period of diuresis. This possibility was pointed out by Calvin,^{13a} who found that the percentage of plasma protein during diuresis with mersalyl increases less than one would expect from the decrease in plasma volume.

SUMMARY AND CONCLUSIONS

The changes in the concentration of hemoglobin and total plasma protein occurring during diuresis after the administration of mercuriophylline were studied in 34 patients receiving 57 injections.

Statistical analysis showed that hemoglobin and plasma protein change in the same direction and that within a period of seven to twenty-eight hours after the injection of mercuriophylline the presence or absence of hemoconcentration is independent of the time of examination. Some observations obtained one to seven hours after the injection indicate that the changes in hemoglobin and total plasma protein were essentially the same as those occurring later.

In cases in which there was edema the average changes in hemoglobin and in total plasma protein observed seven to twenty-eight hours after the injection of mercuriophylline did not differ significantly from 0 in statistical analysis. In cases in which there was not edema there was a significant rise in hemoglobin and total plasma protein seven to twenty-eight hours after the injection. In the cases in which there was not edema the rise in hemoglobin and total plasma protein was higher, with an increasing rate of diuresis. In cases in which there was edema the changes in hemoglobin and total plasma protein were not dependent on the rate of diuresis.

The findings indicate that diuresis effected by mercuriophylline causes a hemoconcentration which in the presence of peripheral edema is compensated by a rapid inflow of interstitial fluid into the blood stream. This interpretation is consistent with the theory of the renal action of mercurial diuretics.

Dr. M. Rachmilewitz and Prof. Dr. R. Bachi made suggestions and criticisms.

CONGENITAL DILATATION OF THE PULMONARY ARTERIAL TREE

Relation to Ayerza's Disease and Primary Pulmonary Arteriosclerosis

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AS A single lesion, unaccompanied by other developmental anomalies, congenital dilatation of the pulmonary artery appears to be an extremely rare condition. For convenience, the occurrence of this solitary congenital malformation of the pulmonary artery will be referred to throughout the remainder of this paper as "isolated congenital dilatation of the pulmonary arterial tree." Several cases have been described, but many of these were reported on the basis of clinical diagnosis without pathologic reports, and others do not meet the criteria which I consider correct for isolated congenital dilatation. These criteria are (*a*) dilatation of the entire pulmonary arterial tree with or without sclerosis; (*b*) hypoplasia of the aorta; (*c*) the absence of other congenital anomalies, such as patent ductus arteriosus or patent interauricular septum, and (*d*) the absence of other primary disease of the heart or lungs and of primary arterial disease such as rheumatism or syphilis. When these criteria are applied to the cases reported in the literature under the name "congenital dilatation of the pulmonary artery," only 4 cases meet the requirements.

Perusal of the literature on other conditions in which dilatation of the pulmonary artery is supposed to be a feature led to the conclusion that some of the cases reported as Ayerza's disease and some of those listed as primary pulmonary sclerosis might well be fitted into the group of cases of isolated congenital dilatation. Nevertheless, the total still would not exceed 10 or 12 cases.

The first mention of congenital pulmonary dilatation was made by Zuber¹ in 1904. He described a case which does not belong to the restricted group under discussion because it showed patency of the ductus arteriosus. Assman's² cases also presented other congenital lesions, but his name is mentioned because he was the first to postulate unequal

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1. Zuber, B.: Ueber einen noch nie beschriebenen Fall von hochgradiger, angeborener Erweiterung der Arteria pulmonalis in toto, *Jahrb. f. Kinderh.* **59**: 30-53, 1904.

2. Assman, H.: *Röntgendiagnostik der inneren Krankheiten*, ed. 4, Leipzig, F. C. W. Vogel, 1929.

division of the truncus arteriosus communis as a possible origin for this condition.

In 1933 Oppenheimer³ reported 8 cases under the title "Idiopathic Dilatation of the Pulmonary Artery." Although only 2 of these were confirmed at autopsy, both showed an enlarged pulmonary arterial tree, a small aorta and hypertrophy of the right ventricle, the pulmonary artery in each case showing "arteriosclerosis without compromising the lumen."

The cases of Smith and others,⁴ Johnson⁵ and Heimann and Posel⁶ showed other associated lesions, or were reported without confirmation at autopsy.

"Enormous" enlargement of the pulmonary artery with a small aorta was reported by Routier and Brumlik,⁷ but the coexistence of chronic pulmonary disease lays these cases open to question, even though the presence of a small aorta supports the likelihood that there was a congenital basis for the dilatation. It is interesting to note that these authors argued against the commonly held view that disease of the lungs gives rise to dilatation of the pulmonary arterial tree; they contended that the congenital anomaly predisposes to chronic affections of the lung. The French workers generally accept the concept of unequal division of the truncus arteriosus communis as the source of atrial septal defect and of pulmonary dilatation, but, since most of their writings deal with the former, their cases are not included. Thus, only one of the cases of both Laubry and others⁸ and Kourilsky and others⁹ falls into the group of isolated congenital dilatation of the pulmonary artery.

Brenner's¹⁰ excellent work on the pathology of the pulmonary vessels contains an analysis of 20 cases of Ayerza's disease, some of which

3. Oppenheimer, B. S.: Idiopathic Dilatation of the Pulmonary Artery, *Tr. A. Am. Physicians* **48**:290-297, 1933.

4. Smith, L. A.; Mœnning, W. P., and Bond, G. S.: Dilatation of the Pulmonary Artery of Congenital Origin, *Radiology* **27**:141-148 (Aug.) 1936.

5. Johnson, S. E.: Congenital Dilatation of the Pulmonary Arteries Revealed by Roentgenkymography, *Ann. Int. Med.* **10**:546-549 (Oct.) 1936.

6. Heimann, H. L., and Posel, M. M.: A Case of Congenital Dilatation of the Pulmonary Artery, *Brit. M. J.* **2**:512 (Oct. 23) 1943.

7. Routier, D., and Brumlik, J.: Dilatation congénitale de l'artère pulmonaire, *Arch. d. mal. du cœur.* **33**:184-186 (March-April) 1940.

8. Laubry, C.; Routier, D., and Heim de Balsac, R.: Grosse pulmonaire: Petite aorte, affection congénitale, *Bull. et mém. Soc. méd. d. hôp. de Paris* **56**: 847-850 (Jan. 16) 1941.

9. Kourilsky, R.; Guede, M., and Regaud, J.: Les dilatations congénitales de l'artère pulmonaire, *Bull. et mém. Soc. méd. d. hôp. de Paris* **56**:772-779 (Jan. 6) 1941.

10. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, *Arch. Int. Med.* **56**:211-237 (Aug.); 457-497 (Sept.); 724-752 (Oct.); 976-1014 (Nov.); 1189-1241 (Dec.) 1935.

showed a large pulmonary artery and a small aorta. He also clearly defined primary pulmonary sclerosis as being sclerosis accompanied by hypertrophy of the right side of the heart, but without other pulmonary or cardiac disease. Of all the reported cases, only 16 were found to fit his definition, and of these, 6 showed moderate pulmonary dilatation. Norris¹¹ reported a case with a large pulmonary artery. DeNavasquez and others¹² published reports of 3 cases in which large sclerotic pulmonary arteries were found, along with a hypertrophic right ventricle in each instance. East¹³ also reported 3 cases of primary pulmonary arteriosclerosis in which large pulmonary arteries were found. It is possible that these 7 cases may have had a congenital origin, although I cannot be as certain of this as are some other authors.

It is thus evident that the literature contains only a very small number of cases that can be definitely identified as isolated congenital dilatation of the pulmonary arterial tree, together with a few others which may or may not be included. Herewith is presented an instance of dilatation of the pulmonary artery accompanied by definite sclerotic change in the pulmonary arterial tree, and without demonstrable lung disease, syphilis, rheumatism, or failure of the left side of the heart. It might, then, have been offered as an example of primary pulmonary arteriosclerosis or as a case of Ayerza's disease, but an attempt will be made to show that it rightfully belongs to the group of cases of isolated congenital dilatation.

REPORT OF A CASE

Clinical Summary.—The patient, a 41 year old white woman, was admitted to the medical service of the Royal Victoria Hospital on June 21, 1944, complaining of dyspnea and palpitations, which she stated had been present for seven years. She stated, too, that at the age of 7 she had been found to have a heart murmur on physical examination. She had not had rheumatic fever. In 1935 a uterine suspension and an appendectomy had been performed. Since 1937 there had been two attacks of circulatory failure. In 1940 the patient first noticed cyanosis of the finger tips. She was admitted to the hospital at that time, and investigation revealed a palpable thrill, systolic in time, and felt all over the precordial region. The heart was enlarged to the right, and there was a systolic murmur at the left sternal border. The blood pressure was 125 systolic and 85 diastolic. Reaction to the Wassermann test was negative. The electrocardiogram showed right axis deviation. Fluoroscopic examination showed a dilated pulmonary conus, pulsa-

11. Norris, R. F.: Primary Pulmonary Arteriosclerosis: Report of Case with Marked Calcification of Pulmonary Arteries, *Bull. Johns Hopkins Hosp.* 59:143-153 (Sept.) 1936.

12. DeNavasquez, S.; Forbes, J. R., and Holling, H. E.: Right Ventricular Hypertrophy of Unknown Origin: So-Called Pulmonary Hypertension, *Brit. Heart J.* 2:177-188 (July) 1940.

13. East, T.: Pulmonary Hypertension, *Brit. Heart J.* 2:189-200 (July) 1940.

tion of the pulmonary vessels and hypertrophy of the right ventricle. The clinical diagnosis was patent ductus arteriosus. The patient was discharged on a regimen of rest. Her course was uneventful until three weeks before the final admission, in June of 1944, when she began to have fever (temperature elevated to 103 F.) and chills. She was put to bed at home, awaiting accommodation in the hospital.

On June 21, the day of admission, the temperature was 102 F., pulse rate 88, respirations 22 and blood pressure 124 systolic and 78 diastolic. The heart presented the same picture as before, and there was cyanosis of the finger tips and toes.



Fig. 1.—Photograph of heart showing the left ventricle and the small aorta. Note also the great hypertrophy of the right ventricle, the cut edge of which is seen at the lower right.

The liver was just palpable. The leukocyte count was 12,400, and the red cell count was 5,200,000. A blood culture on the day of admission yielded 22 colonies of *Streptococcus viridans* per cubic centimeter. The clinical impression was that the patient suffered from bacterial endarteritis in a patent ductus arteriosus.

Sulfonamide therapy was instituted, and the temperature dropped, but soon rose again. The patient was transferred to the department of surgery, where an operation was performed to tie off the ductus arteriosus. The patient's condition deteriorated rapidly, however, and she died in the operating room.

Postmortem Examination.—A complete autopsy was performed three hours after death. In the following summary only the pertinent findings are given in detail.

The heart showed tremendous hypertrophy of the right side (weight, 555 Gm.), and slight dilatation. The valves were essentially normal. The aortic valve ring was small, having a circumference of only 4 cm., and the entire aorta was remarkably small, its circumference averaging about 3.5 cm. (fig. 1). The pulmonary valve ring was large, measuring 7.5 cm. in circumference. The pulmonary artery was definitely larger than normal (8 cm. in circumference, fig. 2), and the



Fig. 2.—Photograph of heart showing the hypertrophied right ventricle and the dilated pulmonary artery.

branches were considerably enlarged out to the periphery of the collapsed lungs. The entire pulmonary arterial tree showed distinct arteriosclerosis, and on section of the lungs, the smaller branches stood out prominently because of their size and thickness (fig. 3). In addition, some of the larger branches were filled with adherent thrombi. The aorta showed only minimal arteriosclerosis. The ductus arteriosus was easily identified, and around it were two heavy silk ligatures. The aortic orifice of the ductus arteriosus was represented only by a "dimple" about which there was some arteriosclerotic change. It admitted the tip of a

probe. There was a smaller "dimple" on the pulmonic side, but there was no communication between the two. There were no vegetations found in relation either to the obliterated ductus or to any of the heart valves. The lungs presented a striking degree of collapse but exhibited no gross evidence of fibrosis or emphysema (fig. 3).



Fig. 3.—Photograph of the posterior halves of both lungs. Dilatation and sclerosis of all the branches of the pulmonary arterial tree can be seen. Some of these vessels are plugged with thrombus material. The lungs are atelectatic.

Microscopic Examination.—The pulmonary aorta and its large and medium-sized branches within the lungs differed strikingly from the normal in the great width of their lumens. It was especially noteworthy that the medial coat of the pulmonary aorta was not thicker than that of the normal pulmonary trunk, and indeed appeared, if anything, somewhat thinner, even in areas where no arteriosclerotic thickening of the intima complicated the picture. So too, in the large

and medium-sized branches of the pulmonary artery the medial coat was conspicuously thin in relation to the large diameter of their lumina (fig. 4). All of these vessels presented numerous areas of arteriosclerotic thickening of the intima, and the largest exhibited the formation of atheromatous cavities in their depths. Beneath such lesions the media was even thinner than elsewhere. In several of the large and medium-sized branches of the pulmonary artery thrombi of varying ages occupied the lumen, seldom, however, obstructing it completely. Most of these thrombi were partly or almost completely organized, but some of them, lying in relation to severe arteriosclerotic intimal lesions, presented hyaline fusion and loss of cellular structure such as to suggest old thrombus material that had not become organized. The surfaces of such thrombi in a few places showed addi-

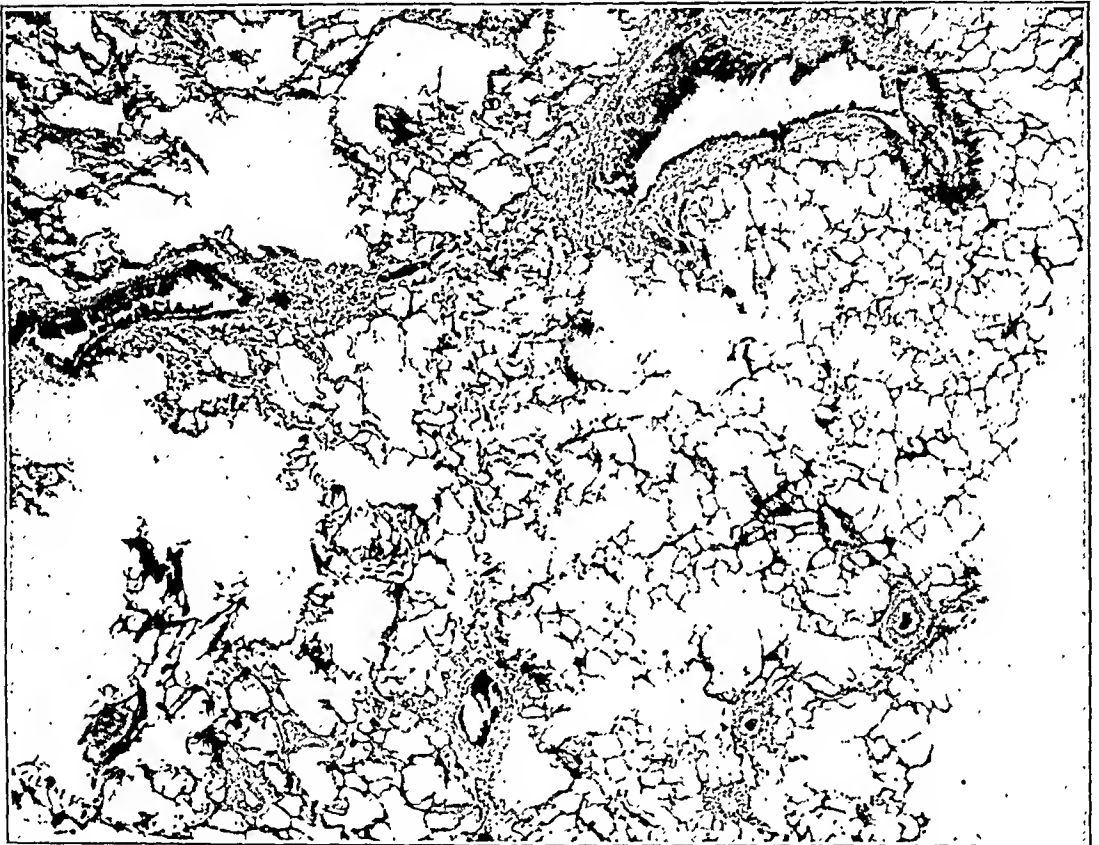


Fig. 4.—Photomicrograph of lung near periphery. Dilatation and sclerosis of small arterial branches are evident ($\times 15$).

tional deposits of fresh thrombus material. The small arteries and arterioles throughout the parenchyma of the lung did not present such an obvious disproportion between the thickness of the media and the size of the lumen even in those vessels that were free from arteriosclerotic thickening of the intima (fig. 4). Such vessels, however, were relatively few in comparison with the large numbers of arteries of this size that were considerably affected by concentric fibrous thickening of the intima. The latter varied in degree from minimal subintimal increase of collagen to a dense fibrous thickening of the intima that reduced the lumen to an extreme degree (fig. 5). Other small arteries were honeycombed with multiple channels lined with endothelium and separated from one another by more or less cellular fibrous connective tissue (fig. 6). This appeared to be the result

of organization and recanalization of thrombus material. The obliterated ductus arteriosus was cut in serial sections, examination of which revealed no trace of a persistent lumen anywhere. The parenchyma of the lungs presented a widespread though moderate degree of atelectasis. In some patches the collapse was complete, giving an appearance of density suggestive of possible fibrosis, but special stains for fibrous connective tissue revealed no significant increase of collagen in these areas or elsewhere in the lung. There was no evidence of emphysema apart from the rupture of a few of the alveolar walls in widely scattered areas. The alveolar spaces were everywhere free from exudate. The liver presented histologically rather slight evidence of chronic passive hyperemia.

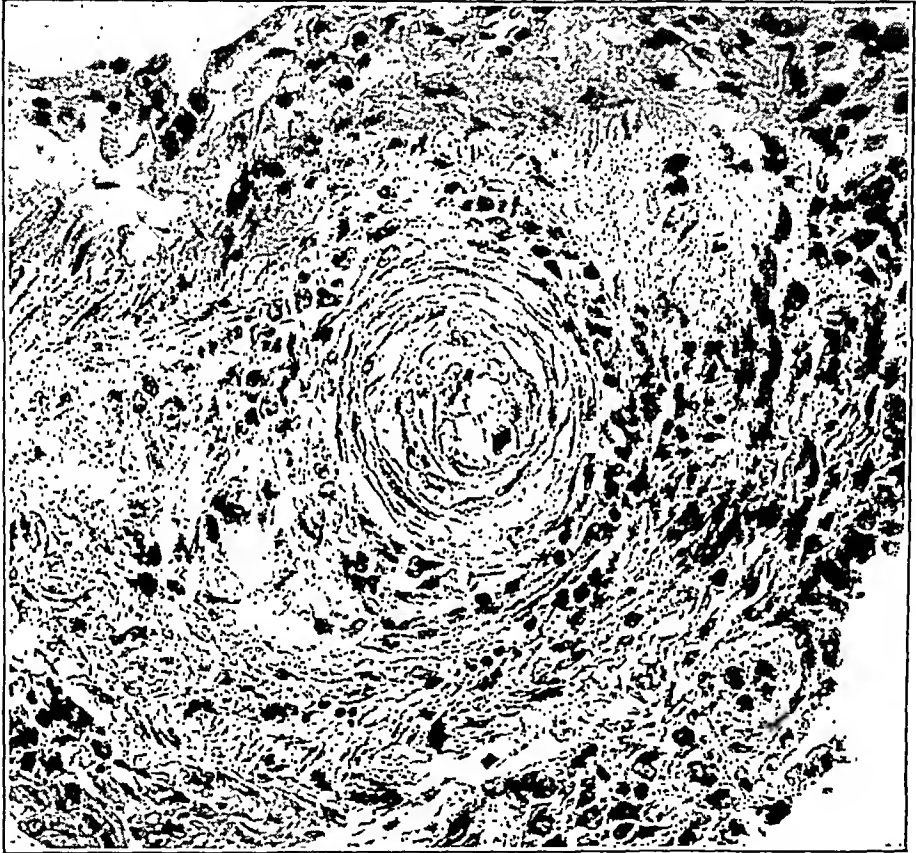


Fig. 5.—Photomicrograph of small artery of lung. Note concentric laminated proliferation of the intimal layer and extreme narrowing of the lumen ($\times 360$).

Bacteriologic Examination.—Postmortem cultures of the heart's blood yielded no growth aerobically or anaerobically.

COMMENTS

It is generally agreed that dilatation of the pulmonary artery is a feature of Ayerza's disease and that dilatation is frequently associated with primary sclerosis of the pulmonary artery. Therefore it is evident, from the foregoing description, that this case might be considered to represent any one of three conditions, namely Ayerza's disease, primary

pulmonary arteriosclerosis or isolated congenital dilatation of the pulmonary arterial tree.

Opinion as to the definition of Ayerza's disease is still extremely varied and confusing. Some authors group all cases of cyanosis, dyspnea and erythrocytosis of pulmonary origin under this term. Some say that the clinical manifestations are correlated with sclerosis of pulmonary vessels due to syphilis. Others believe Ayerza's disease to be due to sclerosis secondary to changes in pulmonary tissue and have written extensively of chronic bronchopulmonary disease as the under-

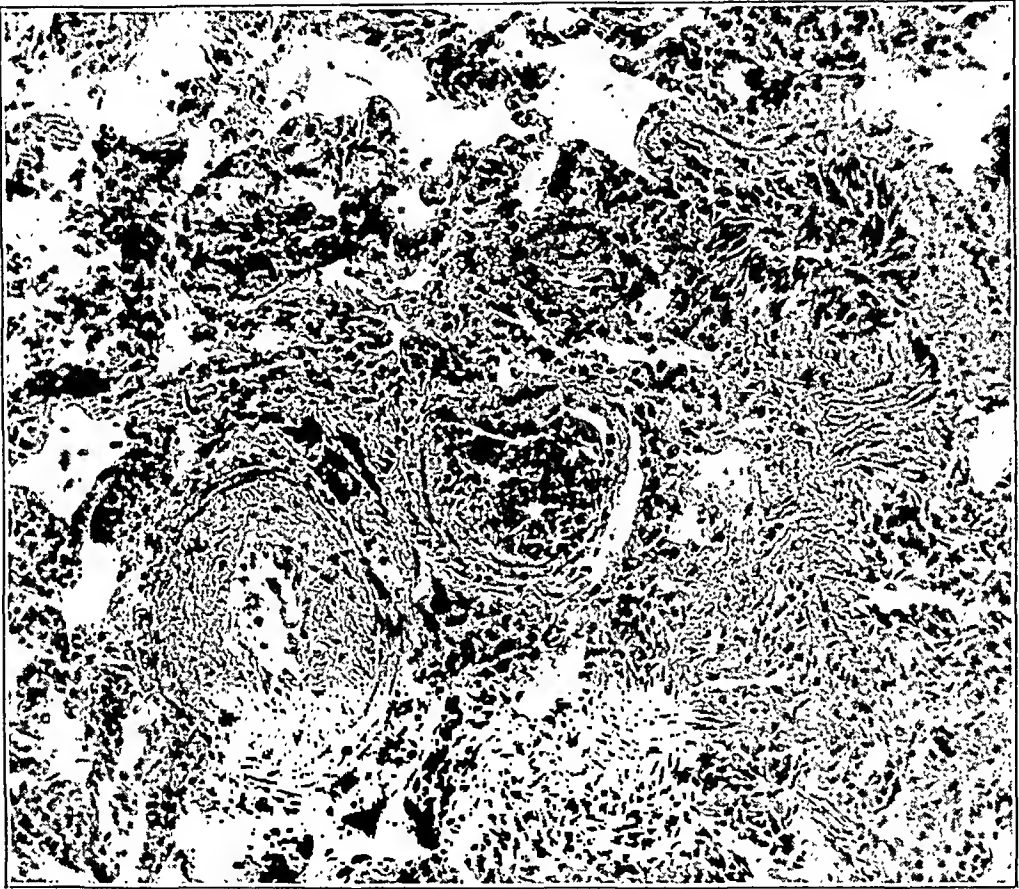


Fig. 6.—Photomicrograph of lung with small arteries showing distinct intimal proliferation. One vessel (at center) presents multiple channels probably produced by recanalization of thrombus ($\times 160$).

lying cause. Brenner¹⁰ collected from the literature 20 cases described under the title of Ayerza's disease. Among these there was, in general, enlargement of the right side of the heart and, to a lesser extent, of the left side of the heart. In some cases there was coronary sclerosis, and in some, mitral stenosis. Besides pulmonary arteriosclerosis there was bronchitis, bronchiectasis, emphysema or pulmonary fibrosis in almost all of the cases. As mentioned previously, some of these cases exhibited a small hypoplastic aorta. Thus, some of the cases reported as Ayerza's

disease are merely examples of secondary sclerosis of the pulmonary artery; others, and these are very few, are cases of primary pulmonary sclerosis, and some very probably are cases of congenital dilatation of the pulmonary arterial tree. Brenner said of Ayerza's disease, "It is clear that there is nothing specific about the symptoms which are ordinarily recognized as being those of heart failure secondary to chronic lung disease . . . there is almost always pulmonary sclerosis which is less marked than in some cases which show no heart symptoms. There is no good reason for retaining the term Ayerza's disease." This is a conclusion in which I heartily concur.

As regards primary pulmonary arteriosclerosis, Brenner concluded that it is not a pathologic entity, but several conditions included under the same name. Although several theories exist as to the cause of the condition, none is universally applicable, and Brenner felt that there must be many causes that could produce the same final morbid picture.

The relation between pulmonary sclerosis, pulmonary hypertension and pulmonary dilatation might well be discussed here. It is probable that raised tension in a pulmonary vessel can give rise to sclerosis, even though this is difficult to prove experimentally. For instance, Karsner, Simon and Fujiwara¹⁴ could not show that hypertension in the pulmonary circuit of experimental animals caused sclerosis of the pulmonary vessels. That sclerosis of the main branches of the pulmonary artery can cause a raised tension is more difficult to believe. Yet it is felt by many that dilatation of the pulmonary arteries can be caused by increased intravascular tension due to pulmonary arteriosclerosis. In mitral stenosis there are often found sclerotic changes in the pulmonary arteries and arterioles of a most severe degree, and yet there is no general dilatation of the pulmonary tree. The example of mitral stenosis can be used also to throw doubt on the belief that raised tension can cause dilatation, because here, besides the presence of sclerosis, there is back pressure in the pulmonary circuit with ensuing pulmonary hypertension. Simon¹⁵ states that in none of his experimental animals in which hypertension was definitely produced in the pulmonary circuit was any dilatation found. It would appear, therefore, that sclerosis and/or raised pulmonary tension is not enough to cause dilatation. It follows from this that in the cases of so-called primary pulmonary arteriosclerosis which do show a high degree of dilatation there must be some additional factor to account for the dilatation.

There appears to be good reason for believing that the dilatation of the pulmonary arteries in such cases is dependent on a congenital dispro-

14. Karsner, H. T.; Simon, M. A., and Fujiwara, T. F.: The Relation of Experimental Pulmonary Arterial Hypertension to Arteriosclerosis, *Arch. Path.* **31**:585-591 (May) 1941.

15. Simon, M. A.: Personal communication to the author.

portion in the size of the pulmonary arterial tree relative to the rest of the vascular system. The outstanding argument for the concept of a congenital origin is the association of a hypoplastic aorta. Cases that show this combination, I am convinced, are definitely congenital in origin. Those instances of dilatation of the pulmonary tree not associated with hypoplasia of the aorta may also be of congenital origin, but the evidence is not so strong in such cases. It seems certain that the large pulmonary artery and small aorta seen in the case reported here are based on an unequal division of the truncus arteriosus communis. The apparent great rarity of this combination as an isolated condition is explained by the fact that it is much more frequently associated with a congenital defect in the interauricular septum, to which the main attention is often directed to the exclusion of interest in the large pulmonary artery. In seeking an explanation for the large size of the pulmonary artery in so many cases of atrial septal defect, Taussig, Harvey and Follis¹⁶ said, "the cause . . . is obscure . . . it appears to be *ipso facto* a congenital malformation which frequently accompanies a defect in the interauricular septum." Again, Laubry and others⁸ and Kourilsky and others⁹ emphasized the importance of unequal division of the truncus arteriosus communis in the development of atrial septal defect. Evidently this unequal division can lead to septal defect, together with congenital dilatation of the pulmonary vessels, or to "isolated" congenital dilatation of the pulmonary arterial tree.

Given a large pulmonary artery and a small aorta as a congenital malformation, how does the former become sclerotic? It is well known that when there is a column of fluid at constant pressure in a cylinder, the stress or stretching force at any point in the wall of the cylinder is directly proportional to the diameter of the column. Therefore, with the same internal pressure, the stress or stretching force on the wall of a large vessel is greater than that on a small one, and the stress on a dilated vessel wall is greater than it would be were the diameter of the vessel normal. To withstand successfully the increased stress, the wall of the dilated vessel would have to be thicker in proportion to the increase of its diameter, and there is no evidence to indicate that in the present case the dilated pulmonary arteries were thicker than normal before the arteriosclerosis developed. If one accepts the hypothesis that arteriosclerosis is a degenerative lesion which may be initiated by the mechanical effects of an increased stress on the vessel wall,¹⁷ then the development

16. Taussig, H. B.; Harvey, A. M., and Follis, R. H., Jr.: The Clinical and Pathological Findings in Interauricular Septal Defect: Report of Four Cases, *Bull. Johns Hopkins Hosp.* 63:61-89 (Aug.) 1938.

17. Moschcowitz, E.: *Vascular Sclerosis*, London, Oxford University Press, 1942.

of arteriosclerosis in the congenitally dilated pulmonary tree is adequately explained. Abnormal stretching forces in the wall of a vessel may originate from increased diameter of the vessel alone without the necessity of increased hydrostatic pressure, and that is the crux of the argument.

Accordingly, the case presented here is interpreted as having included initially only a congenital malformation in the form of dilatation of the pulmonary arterial tree without proportionate increase in the thickness of the media of the dilated vessels. This condition exposed the unduly thin walls to abnormal stretching forces, which initiated arteriosclerotic changes in the absence of pulmonary hypertension. Eventually, obstruction of some of the large and medium-sized pulmonary arteries by thrombus material and of small arteries by encroachment of arteriosclerotic intimal thickening on their lumens led to increased pulmonary pressure, right-sided cardiac hypertrophy, and final cardiac failure under the stress of a major surgical procedure.

The existence of primary pulmonary arteriosclerosis cannot be questioned, and those cases which show slight dilatation of the pulmonary arteries, sclerosis of no apparent cause and right-sided cardiac hypertrophy must be classed together, and their cause and pathogenesis left a question. However, some of the cases reported under this heading, in which the pulmonary vessels are dilated, including Brenner's case 2, probably have a congenital origin. Pulmonary arteriosclerosis can exist to a considerable degree without hypertrophy of the right side of the heart and is therefore, by Brenner's definition, not primary pulmonary arteriosclerosis. This fact suggests that the hypertrophy in primary pulmonary arteriosclerosis may be as primary as the sclerosis itself, both having a common unknown cause (Brenner¹⁰). As regards isolated congenital dilatation, the French workers are of the opinion that the hypertrophy of the right side of the heart in these cases also has a congenital basis, the same developmental imbalance giving rise to the dilated pulmonary artery, the small aorta and the disproportionate size of the right side of the heart. Congenital dilatation of the pulmonary artery might be classified as a subgroup of primary pulmonary sclerosis, and this is in agreement with Brenner's idea that primary sclerosis is several conditions included under one name.

As regards the clinical picture, Bedford, Papp and Parkinson¹⁸ grouped primary pulmonary arteriosclerosis with congenital pulmonary dilatation under the term "primary dilatation." They stated that in advanced stages the clinical picture is identical with that of atrial septal defect and that differential diagnosis may be impossible during life. As

18. Bedford, D. E.: Papp, C., and Parkinson, J.: Atrial Septal Defect, *Brit. Heart J.* 3:37-68 (Jan.) 1941.

has been seen from the present case, the two conditions may also be easily confused with patency of the ductus arteriosus. In 1943 Grishman, Steinberg and Oppenheimer¹⁹ reported their work on angiocardiology and said that by this means they could make the diagnosis during life with a fair degree of certainty. Accurate clinical diagnosis, of course, is important, in view of the growing feasibility of the operative treatment for patency of the ductus arteriosus.

SUMMARY AND CONCLUSIONS

1. The name "isolated congenital dilatation of the pulmonary arterial tree" is suggested as a term to indicate the occurrence of this condition in the absence of other congenital malformations in the circulatory system with the single exception of a hypoplasia of the aorta, which is a frequent corollary to the largeness of the pulmonary arterial system.

2. The great rarity of this condition is demonstrated by a review of the literature.

3. A case that presented a dilated arteriosclerotic pulmonary tree and a hypoplastic aorta is reported.

4. Discussion of Ayerza's disease and of primary pulmonary arteriosclerosis in relation to isolated congenital dilatation of the pulmonary arterial tree leads to the conclusion that the case presented is an example of the latter condition.

5. A theory to explain the development of arteriosclerosis in the congenitally dilated pulmonary tree is suggested.

6. The clinical features of the condition under consideration are briefly indicated.

19. Grishman, A.; Steinberg, M. F., and Oppenheimer, B. S.: The Clinical Diagnosis of Idiopathic Dilatation of the Pulmonary Artery, *J. Mt. Sinai Hosp.* **10**:142-149 (May-June) 1943.

Progress in Internal Medicine

GASTROENTEROLOGY

A Review of the Literature from July 1944 to June 1945

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INTRODUCTION

THE NUMBER of articles published from July 1944 to June 1945 is surprisingly large when one recalls that this period represents the peak of the war effort. There was a significant increase in the attention given military gastroenterology, but civilian gastroenterology continued to receive nevertheless the main emphasis.

Developments in the physiology of the digestive tract during 1943 and 1944 have been reviewed by Babkin and Friedman¹; Breitwieser and Miller² have discussed recent advances in the entire field of gastroenterology. Clark³ in a good discussion of abdominal pain emphasizes the frequency with which diaphragmatic hernia, disease of the gallbladder and functional derangements of the digestive tract may mimic or accentuate cardiac disease or its symptoms; Scott⁴ brings out the reverse condition.

Brennemann's⁵ review of abdominal pain in children is a classic to be read with profit by every one interested in the subject. His final comment is of particular interest: "In conclusion I can only say that the majority of abdominal pains encountered in private practice, which gives a truer picture of actual incidence than is found in hospital practice,

From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

1. Babkin, B. P., and Friedman, M. H. F.: Digestive System, in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1945, vol. 7, pp. 305-330.

2. Breitwieser, E. R., and Miller, T. G.: Recent Advances in Gastro-Enterology, M. Clin. North America 28:1349-1361, 1944.

3. Clark, W. E.: Gastrointestinal Conditions Simulating or Aggravating Cardiovascular Disease, J. A. M. A. 128:352-355 (June 2) 1945.

4. Scott, J. W.: Gastrointestinal Symptoms in Cardiovascular Disease, Canad. M. A. J. 52:128-130, 1945.

5. Brennemann, J.: Abdominal Pain in Children, J. A. M. A. 127:691-695 (March 24) 1945.

have in my experience, been of unknown nature and unknown etiology." Campbell⁶ calls attention to the frequency with which urologic disease may cause abdominal pain in children. Strauss⁷ in a discussion of the differential diagnosis of abdominal pain in children stresses the difficulty caused by the confusing of the exanthems with mesenteric lymphadenitis or with appendicitis, by the presence of gastrointestinal anomalies and by the fatty condition of the abdomen so often encountered in young children, which hinders proper abdominal palpation and percussion. Allen⁸ gives an excellent review of the present status of abdominal surgery.

Aaron⁹ summarizes the various drugs used in the treatment of gastrointestinal conditions and the best methods of administration and reviews the treatment of inflammatory lesions of the upper part of the gastrointestinal tract. Gray¹⁰ discusses the role in gastrointestinal disease of occupational hazards, including metal intoxications, such as lead, arsenic and mercury poisoning and solvents, such as carbon tetrachloride, benzene, the chlorinated naphthalenes and diphenyls; McGee, McCausland, Preston and Houff¹¹ describe the disturbances resulting from trinitrotoluene intoxication.

Gibb¹² reviews his gastroenterologic experience in a large rear area naval hospital and concludes that it approximated that of civilian life.

ANOREXIA NERVOSA AND FUNCTIONAL DISORDERS

Berkman¹³ notes again that patients with anorexia nervosa are not concerned by their loss of weight or their cachectic appearance and evade a discussion of the emotional factors precipitating the anorexia or the vomiting. Amenorrhea occurred in 50 per cent of his cases, but there were no recognizable avitaminoses. In women over 30, the

6. Campbell, M. F.: Abdominal Pain Due to Urologic Disease in Children, *J. A. M. A.* **128**:326-329 (June 2) 1945.

7. Strauss, A. A.: Abdominal Pain in Children from a Surgical Standpoint, *J. A. M. A.* **128**:330-335 (June 2) 1945.

8. Allen, A. W.: Medical Progress in Abdominal Surgery, *New England J. Med.* **232**:165-173, 1945.

9. Aaron, A. H.: Comment on Drugs Frequently Used in the Treatment of Gastrointestinal Conditions, *Clinics* **3**:663-671, 1944; Inflammatory Lesions of the Upper Gastrointestinal Tract, *J. A. M. A.* **127**:1027-1030 (April 21) 1945.

10. Gray, I.: Gastrointestinal Disease in Relation to Occupational Hazards, *Gastroenterology* **4**:61-71, 1945.

11. McGee, L. C.; McCausland, A.; Preston, J. F., Jr., and Houff, L. A.: Metabolic Disturbances in Workers Exposed to Trinitrotoluene, *Gastroenterology* **4**:72-82, 1945.

12. Gibb, W. T.: Gastroenterology in a Large Naval Hospital, *South. M. J.* **37**:507-510, 1944.

13. Berkman, J. M.: Anorexia Nervosa: The Diagnosis and Treatment of Inanition Resulting from Functional Disorders, *Ann. Int. Med.* **22**:679-691, 1945.

incidence of the disease is low, but the therapy is more difficult. Treatment consists in discussion of the emotional factors and consumption of a high protein diet adjusted to the caloric needs of the patient, in which the number of calories is increased by 300 every five to six days. The mechanism and the significance of the amenorrhea should be discussed with the patients.

Rush¹⁴ discusses the recognition and the treatment of anxiety neuroses presenting predominantly gastrointestinal symptoms in an overseas army hospital and describes some instructive cases. "The early recognition and treatment of these patients is the most important factor in preventing the establishment of a permanent neurosis." Carleton's¹⁵ experience in the Navy was similar.

Alvarez¹⁶ emphasizes how little is known even today about the nature, the origin, the mode of production and the significance of the common symptoms physicians are constantly called on to relieve. Heartburn consists of a burning (sometimes painful) or rending distress located usually under the lower end of the sternum and running up as far as the pharynx. Few of the 123 patients with heartburn had any organic disease of the digestive tract. In 17 patients who had or had had ulcer it was noted that when the ulcer was active and hunger pain was present heartburn was absent. Conversely, when heartburn was present, the ulcer seemed to be healed. Heartburn usually comes in "spells" lasting from days to weeks, months or years. The degree of acidity of the gastric content is not important.

Alvarez¹⁷ also describes 2 cases of a rare syndrome resembling the gastric crisis of tabes and related to that seen in "nervous bloaters." One of the patients, a woman, suffered for years from frequent and very painful "spells" which came suddenly, lasted a few hours and disappeared suddenly. During the "spell" the abdominal wall was flat and boardlike; severe, labor-like pains came and went every four minutes or so. There was nothing else to suggest any disturbance of function of the digestive tract. Morphine in doses of 1 or 2 grains (0.065 or 0.13 Gm.) had little effect on the pain but somewhat shortened the spells. Exploratory operations and a necropsy failed to reveal any cause for the disease. The second patient, also a woman, who appeared to have hysterical tendencies and lived a stormy life with a dipsomaniac, suffered for years from spells resembling those of the

14. Rush, A.: The Anxiety Neuroses Manifested by Gastrointestinal Symptoms, *M. Clin. North America* 28:1541-1543, 1944.

15. Carleton, W. T.: Gastrointestinal Tract Disturbances: Functional Disturbances on a Psychogenic Basis, *U. S. Nav. M. Bull.* 44:538-548, 1945.

16. Alvarez, W. C.: Heartburn, *Gastroenterology* 3:1-12, 1944.

17. Alvarez, W. C.: A Rare Syndrome of Crisislike Abdominal Pain, *Gastroenterology* 4:296-304, 1945.

first woman, with the difference that she bloated distressingly and sometimes retched. On one occasion an attack began with spasm only of the muscles in the left upper quadrant of the abdomen. At times when the woman's attention was distracted by vomiting, the abdominal muscles relaxed and the bloating disappeared, only to reappear instantly when her abdomen was touched and her attention drawn to it. The clinical picture appeared to represent a link between that presented by the first type of patient and that of the "nervous bloaters" who have no gas in the bowel. The diagnosis of hysteria seems acceptable in the second case, less so in the first one.

Brooke¹⁸ reports 4 cases of massive gastrointestinal hemorrhage occurring one to four days after a minor surgical operation and considered to be nervous in origin. However, in 1 patient the roentgenographic findings were considered compatible with duodenal ulcer; negative findings were reported in 2; the fourth had no roentgenologic examination. Gastroscopic studies were not made. [The reviewers are unable to accept these as bona fide instances of hemorrhage on a "psychic or emotional basis."]

ESOPHAGUS

Review.—Benedict¹⁹ analyzes 30 papers dealing with diseases of the esophagus and published during the years 1942 and 1943.

Roentgenologic Appearance.—In a beautifully illustrated article, Calthrop²⁰ demonstrates the great value of the examination. Bakwin, Galenson and LeVine²¹ show that in infants the esophagus is a distensible tube as wide or wider than the vertebral column.

Anomalies.—Ladd and Scott²² in an excellent paper present the anomalies and the problems encountered in the treatment of 5 patients. Esophageal duplications of developmental origin may form mediastinal cysts along the course of the esophagus. These cysts have muscular walls and mucous membrane linings simulating gastric mucosa and subject to peptic ulceration. Surgical extirpation is best accomplished by

18. Brooke, P. A.: Gastrointestinal Bleeding on a Psychic or Emotional Basis Following Minor Surgical Procedures, *Clinics* 3:997-1002, 1944.

19. Benedict, E. B.: Esophagus: Review of Literature 1942 and 1943, *Gastroenterology* 3:90-97, 1944.

20. Calthrop, G. T.: Radiology in Diseases of the Oesophagus, *Post-Grad. M. J.* 20:282-286, 1944.

21. Bakwin, H.; Galenson, E., and LeVine, B. E.: Roentgenographic Appearance of the Esophagus in Normal Infants, *Am. J. Dis. Child.* 68:243-247 (Oct.) 1944.

22. Ladd, W. E., and Scott, H. W., Jr.: Esophageal Duplications or Mediastinal Cysts of Enteric Origin, *Surgery* 16:815-835, 1944.

marsupialization and subsequent destruction of the mucosal lining. Three of the 5 patients recovered.

Haight²³ analyzes the findings in 32 patients with congenital atresia. In all the upper segment ended as a blind pouch. Twenty-six had a communication between the lower esophageal segment and the trachea or a bronchus. A primary anastomosis of the upper and lower esophageal segments was done in 16 of the 24 patients for whom an exploration of the anomaly was undertaken. Six, or 37.5 per cent, of the 16 patients are living, seven months to three years after operation—the best results obtained thus far with this operation. The reconstructed esophagus is patent in all instances.

Daniel Jr.²⁴ reports 7 cases of congenital atresia. An end to end anastomosis was successfully performed in 1. Four additional cases are reported, with survival of seven months in 1.²⁵

Fistula.—Moersch and Tinney²⁶ report 39 cases of acquired fistula between the esophagus and the tracheobronchial tree: In 36 per cent it was due to carcinoma of the esophagus; in 13 per cent, to trauma; in 10 per cent, to syphilis; in 10 per cent, to tuberculosis, and in 5 per cent, to diverticulosis of the esophagus. Death is usually the result of aspiration pneumonia or of mediastinal or pulmonary abscesses. Surgical measures may be of value, particularly in those instances in which the fistula is a result of trauma.

Aneurysm.—A syphilitic aneurysm of the aorta that ruptured into the esophagus is reported.²⁷

Rupture.—Another instance of spontaneous rupture of the esophagus occurring after a heavy meal is described, apparently the third case to be diagnosed before death!²⁸ A longitudinal tear three fourths of an inch long (about 2 cm.), beginning an inch above the diaphragm, was repaired surgically, but the patient died within twenty-four hours.

23. Haight, C.: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula: Reconstruction of Esophageal Continuity by Primary Anastomosis, *Tr. Am. Surg. A.* **62**:623-655, 1944; *Ann. Surg.* **120**:623-655, 1944.

24. Daniel, R. A., Jr.: Congenital Atresia of the Esophagus, with Tracheo-Esophageal Fistula, *Ann. Surg.* **120**:764-771, 1944.

25. Singleton, A. O., and Knight, M. D.: Congenital Atresia of the Esophagus, with Tracheo-Esophageal Fistulae: Transpleural Operative Approach, *Tr. South. S. A.* (1943) **55**:267-283, 1944.

26. Moersch, H. J., and Tinney, W. S.: Fistula Between the Esophagus and the Tracheobronchial Tree, *M. Clin. North America* **28**:1001-1007, 1944.

27. Bernstein, B. M.; Slater, S. R., and Grayzel, D. M.: Perforation of the Aorta into the Alimentary Tract: Case Report, *Clinics* **3**:447-449, 1944.

28. Collis, J. L.; Humphreys, D. R., and Bond, W. H.: Spontaneous Rupture of the Oesophagus, *Lancet* **2**:179, 1944.

Stricture.—Esophageal stenosis spontaneously perforating into the mediastinum caused death in a 7 month old baby who had accidentally ingested at the age of 1 month a drachm (about 2 Gm.), of lactic acid.²⁹ Crowe³⁰ analyzes the treatment of 57 patients with injuries caused by lye. Fifty-two (89 per cent) were under 5 years of age. Immediate lavage of the esophagus with weak acids and olive oil is recommended, followed by early prophylactic dilation with the Bokay method in all patients found by roentgenologic examination to have esophageal involvement. Of 13 such patients, 9 did not undergo stricture. Delay in treatment necessitates more drastic measures, accompanied by an 8 per cent mortality, but careful attention to the prevention of secondary stricture and long-continued dilation produced good results in the other 92 per cent.

Campbell³¹ describes the case of a 14 year old boy in whom at the age of 5 years stricture of the lower part of the esophagus gradually developed, of unknown cause. Gastrostomy was performed. By the ingenious device of passing a needle threaded with silk through an esophagoscope placed in the stomach through the gastrostoma, the needle was also passed through the obstruction into another esophagoscope lying in the upper part of the esophagus and the thread thus brought out through the mouth. With this used as a guide, larger strings were gradually introduced and the area was canalized. Retrograde bouginage finally accomplished sufficient dilation to allow the passage of food and permit closure of the gastrostoma.

Scleroderma.—Richieri and d'Alotto³² describe another instance of scleroderma and a short esophagus.

Ulcer.—The roentgenologic diagnosis is discussed, and 2 additional cases are reported.³³ Fatal perforation and bleeding from an esophageal ulcer occurred in a child following a burn.³⁴

29. Trainer, J. B.; Krippachne, W. W.; Hunter, W. C., and Lagozzino, D. A.: Esophageal Stenosis Due to Lactic Acid, *Am. J. Dis. Child.* **69**:173-175 (March) 1945.

30. Crowe, J. T.: Poisoning Due to Lye: Value of Bokay Prophylactic Dilation in Prevention of Early Strictures of the Esophagus, *Am. J. Dis. Child.* **68**: 9-12 (July) 1944.

31. Campbell, A. A.: Canalization of Complete Oesophageal Stricture (Report of Case), *Bull. Acad. Med., Toronto* **18**:166-172, 1945; *Canad. M. A. J.* **52**:471-474, 1945.

32. Richieri, A., and d'Alotto, V.: Esófago corto y estómago torácico en una esclerodermia, *Prensa méd. argent.* **31**:2331-2333, 1944.

33. Lust, F. J., and Peskin, A. R.: Roentgenologic Diagnosis of Peptic Ulcer of the Esophagus, *Am. J. Roentgenol.* **52**:40-45, 1944.

34. Rankin, L. M.: Perforated Ulcer of Esophagus Following a Burn, *Am. J. Surg.* **67**:134-136, 1945.

Cardiospasm.—Hurst and Bassin³⁵ describe 11 cases of megaesophagus, which they diagnosed roentgenologically by means of mediastinal widening before giving a barium sulfate meal.

Three papers have appeared describing the pulmonary complications: abscess, aspiration pneumonitis, fibrosis and bronchiectasis. Megaesophagus with pulmonary complications may exist with slight, or indeed with no, symptoms referable to the esophagus.³⁶

Field,³⁷ having studied the efficacy of amyl nitrite, glyceryl trinitrate and octyl nitrite in producing relaxation of the cardia, found that octyl nitrite possesses the following advantages: Its odor is more pleasant than that of amyl nitrite; it can be administered in an inhaler; it acts more rapidly than glyceryl trinitrate, and the inhaler dosage can be regulated more easily. [The reviewers have used octyl nitrite in a limited number of relatively early cases of cardiospasm, with encouraging results to date.]

Reports of the successful surgical treatment of cardiospasm continue to appear.³⁸

Carcinoma.—The reported annual mortality from carcinoma of the esophagus is about 1,600 in England and Wales and about 2,000 in the United States. At autopsy 25 to 40 per cent of the carcinomas do not show metastases.³⁹ In 1,564 routine autopsies on male British West Indian and Panamanian Negroes, 35 (2.3 per cent) were found to have carcinoma of the esophagus, whereas in 591 autopsies on females the incidence was less than 1 per cent.⁴⁰ In a series of 3,048 unselected autopsies on adults, there were 599 cases of carcinoma, and in 19 (3.2 per cent) there was secondary involvement of the esophagus by carcinoma. In these 19 cases plus 7 others the primary sites were as follows: trachea or bronchus (8), stomach (7), larynx (4), breast (2), pancreas

35. Hurst, A., and Bassin, S.: Mega-Esophagus as a Cause of Mediastinal Widening, *Am. J. Roentgenol.* **52**:598-606, 1944.

36. Hawes, L. E., and Soule, A. B., Jr.: Pulmonary Changes in Cardiospasm, *Am. J. Roentgenol.* **53**:124-128, 1945. Bird-Acosta, I.: Pulmonary Suppuration Secondary to Cardiospasm, *ibid.* **52**:481-486, 1944. Weems, H. S.: Pulmonary Disease Associated with Mega-Esophagus, *ibid.* **52**:473-480, 1944.

37. Field, C. E.: Octyl Nitrite in Achalasia of the Cardia, *Lancet* **2**:848-851, 1944.

38. Maingot, R.: Extramucous Oesophagocardiomyotomy in Cardiospasm, *Post-Grad. M. J.* **20**:278-282, 1944. Ferrari, R. C., and Correa Iturraspe, M.: La esofagostomía por vía torácica en el tratamiento del megaesófago, *Prensa méd. argent.* **31**:2089-2101, 1944.

39. Brock, R. C.: The Surgical Treatment of Carcinoma of the Oesophagus, *Post-Grad. M. J.* **20**:287-293, 1944.

40. Tomlinson, W. J., and Wilson, L. A., Jr.: Esophageal Carcinoma in British West Indian and Panamanian Negroes: A Study of the Incidence, Etiologic Factors and Pathologic Anatomy in Fifty Cases, *Arch. Path.* **39**:79-80 (Feb.) 1945.

(2), testes (1), mediastinal lymph nodes (1), undetermined (1).⁴¹ Carcinoma constituted a complication of esophageal diverticulum in 2 (1.08 per cent) of 185 cases.⁴²

Colledge⁴³ in discussing carcinoma of the upper third of the esophagus concludes that "operation is clearly justifiable in early, carefully selected cases, but these are very few and are likely to remain so, and both from the point of view of palliation and possibility of radical cure irradiation is far more frequently the method of choice." Several patients treated more or less successfully by surgical procedure and by irradiation are described. In a group of 38 patients treated palliatively by Patterson and Rouse⁴⁴ by means of intraesophageal and extraesophageal irradiation with dilation, 15 were benefited and 10 survived an average of fourteen and a half months after the diagnosis was made.

Holland⁴⁵ in an interesting discussion of multiple carcinoma presents a case in which there were four independent lesions, all cured, two by surgical and two by roentgen therapy. After five years there was no evidence of recurrence of the esophageal carcinoma treated by roentgen irradiation.

Lymphoma.—A case of cancerous lymphoma (clasmatocytic type) of the esophagus, the mediastinum and the retroperitoneal lymph nodes is presented.⁴⁶

STOMACH

Review.—Mateer and his associates⁴⁷ have prepared an excellent analysis of the current literature on gastric disease, reviewing 124 articles.

Gastric Secretion.—Hollander's⁴⁸ excellent exposition of the various measures of acidity used at the present time by clinical and

41. Toreson, W. E.: Secondary Carcinoma of the Esophagus as a Cause of Dysphagia, *Arch. Path.* **38**:82-84 (Aug.) 1944.

42. Hoover, W. B.: Carcinoma Associated with Esophageal Diverticulum: Report of a Case, *S. Clin. North America* **25**:707-712, 1945.

43. Colledge, L.: Carcinoma in the Upper Third of the Oesophagus, *Post-Grad. M. J.* **20**:294-297, 1944.

44. Patterson, C. O., and Rouse, M. O.: The Treatment of Esophageal Neoplasms: Plea for Active Therapy Plus Minimum Confinement, *South. M. J.* **38**:140-144, 1945. Patterson, C. O.; Rouse, M. O., and Bagwell, J. S.: Medical Management of Common Esophageal Disorders, *Texas State J. Med.* **40**:284-290, 1944.

45. Holland, C. A.: Multiple Carcinomas: A Case of Four Consecutive Primary Carcinomas with Apparent Cure, *J. A. M. A.* **128**:356-359 (June 2) 1945.

46. Cabot Case 31171, *New England J. Med.* **232**:481-484, 1945.

47. Mateer, J. G.; Baltz, J. I.; Comanduras, P. D.; Steele, H. H., and Brouwer, S.: Diseases of the Stomach: A Review of Current Literature, *Gastroenterology* **3**:360-379, 1944.

48. Hollander, F.: What Is p_H ? An Explanation of the Various Measures of Acidity Employed in Gastroenterology, *Gastroenterology* **4**:497-508, 1945.

experimental workers in gastroenterology will interest all those not familiar with recent advances in chemical nomenclature. The advantages of the p_H system of notation are listed: First and foremost, it affords a way of representing and measuring acidities so low that they cannot be determined by titration methods, but which nevertheless are exceedingly important physiologically; second, many physiologic phenomena vary with the acidity, but the relation can be explained more simply in terms of the p_H units than of any of the other systems of notation; third, ionic concentrations other than of hydrogen can be expressed by a similar unit, the concentration of OH ions, for instance, being written p_{OH} and bearing in a solution a simple inverse relation to the concentration of hydrogen ions; finally, the p_H notation has given a convenient way of representing the minute numbers which describe acidities and alkalinities within the physiologic range.

Bull and Gray⁴⁹ discuss the mechanism of the formation of hydrochloric acid and suggest a new theory. A membrane lining the intracellular canaliculus of the parietal cell is thought to be impermeable to cations and at the same time permeable to anions. An organic acid, pyruvic or lactic, is produced in localized areas in the parietal cells. The anions of this acid are exchanged for chloride ions across the cation-impermeable membrane lining the canaliculus. The organic anion is destroyed by decarboxylation within the parietal cell, thus maintaining the necessary gradient of the organic anion.

Dyer and Kelly⁵⁰ compared, in 8 dogs in which gastric fistula had been produced, the secretory response to single injections of molecular equivalents of mecholyl and histamine. Their observations support the theory that mecholyl stimulates the secretion of both pepsin and acid, whereas histamine stimulates chiefly the acid and the volume of secretion. Grossman, Roth and Ivy⁵¹ found that the output and the concentration of pepsin in response to caffeine are approximately the same as those in response to histamine for the first seventy minute period, but are sustained longer. If simultaneously caffeine is administered orally and histamine subcutaneously, pepsin is secreted in an amount greater than the sum of the amounts secreted in response to these drugs administered individually, provided a period

49. Bull, H. B., and Gray, J. S.: Secretion of Hydrochloric Acid by the Stomach, *Gastroenterology* 4:175-182, 1945.

50. Dyer, H. M., and Kelly, M. G.: Gastric Function of Dogs After Stimulation with Acetyl- β -Methylcholine Chloride and Histamine Diphosphate, *J. Nat. Cancer Inst.* 5:227-232, 1944.

51. Grossman, M. I.; Roth, J. A., and Ivy, A. C.: Pepsin Secretion in Response to Caffeine, *Gastroenterology* 4:251-256, 1945.

longer than seventy minutes is studied. In cats and in man the gastric secretory response to histamine or to alcohol is greatly enhanced and prolonged after the administration of caffeine as compared with the output of hydrochloric acid or gastric juice provoked by histamine or alcohol before caffeine is administered. The response to histamine or alcohol and caffeine administered simultaneously is considerably greater than the sum of the individual responses.⁵²

Gillman⁵³ compared the neutral red excretion and the acid secretion of 90 normal persons and found that, whereas the latter fluctuated considerably in the same subject, the excretion of neutral red remained remarkably constant. In a series of 300 persons considered to have "gastric dysfunction" the neutral red test appeared more sensitive. Nasio⁵⁴ reports that a 1 or 2 per cent solution of the hydrochloride of 2-benzyl-4,5-imidazoline (Priscol) given through a tube with 300 cc. of distilled water is a satisfactory stimulant of gastric secretion, although not so good as histamine; parenteral injection provides results similar to those with histamine.

It is surprising to find that nausea and retching inhibit even histamine-induced secretion in subcutaneously transplanted pouches and in vagally denervated pouches of dogs. Abdominal splanchnicectomy and lumbar sympathectomy do not abolish the effect.⁵⁵

The failure of other workers to confirm the work of Andrus and his associates with regard to the inhibiting effect on gastric secretion of jejunal tissues transplanted to the stomach was noted last year. Andersen, Slutzky and Maertz⁵⁶ have now published another such failure, as have Kolouch, Dubus and Wangenstein,⁵⁷ and also Gross-

52. Roth, J. A., and Ivy, A. C.: The Synergistic Effect of Caffeine upon Histamine in Relation to Gastric Secretion, *Am. J. Physiol.* **142**:107-113, 1944.

53. Gillman, T.: A Critical Evaluation of the Neutral Red Excretion and Acid Secretion Tests of Gastric Function in the Normal and in Subjects with Gastric Disorders, *Gastroenterology* **3**:188-205, 1944.

54. Nasio, J.: A New Test for Gastric Function, *Am. J. Digest. Dis.* **11**:227-229, 1944.

55. Grossman, M. I.; Woolley, J. R.; Dutton, D. F., and Ivy, A. C.: The Effect of Nausea on Gastric Secretion and a Study of the Mechanism Concerned, *Gastroenterology* **4**:347-351, 1945.

56. Andersen, A. C.; Slutzky, B., and Maertz, R. W.: Effect on Gastric Secretion of Pedicle Jejunal Grafts in the Wall of the Stomach, *Gastroenterology* **4**:323-331, 1945.

57. Kolouch, F., Jr.; Dubus, A. T. S., and Wangenstein, O. H.: Symposium on Ulcer Problem: The Pedicled Jejunal Transplant onto the Gastric Wall; Evaluation of Its Effect upon Gastric Acidity and Failure of Such Transplants to Afford Protection Against Ulcer Provoked by Histamine in Beeswax, *Surgery* **17**:667-685, 1945.

man, Dutton and Ivy.⁵⁸ A jejunal pedicle graft implanted in the wall of the stomach or jejunal washings perfused through the stomach do not significantly alter the acid-secretory response of the stomach to stimulation with histamine in the dog.

In 19 patients with duodenal ulcer Dragstedt and his associates⁵⁹ observed that the night secretion averaged 820 cc., with free acidity between 24 and 82 clinical units; after transthoracic vagotomy the quantity decreased to an average of 415 cc., with free acidity between 0 and 61 clinical units. No significant difference in the response to histamine was noted. Using the balloon technic, they demonstrated hypermotility and hypertonicity of the empty stomach of the patient with peptic ulcer. Bilateral vagal section decreased the gastric tonus and the hunger contractions.⁶⁰

Babkin and his associates⁶¹ found that in dogs resection of the pyloric part of the stomach temporarily inhibits the action evoked by faradic stimulation of the vagus nerve and changes the character of the gastric juice from water-clear to mucoid. This work seems to support the view of those who think it essential to remove the pylorus in performing subtotal gastrectomy for peptic ulcer. [The reviewers are of the opinion that further controls and repetition of the experiments are needed.]

Acid introduced into the small intestine of the Pavlov pouch dog inhibits gastric secretion in response to a meal, provided an adequate degree of intestinal acidity is attained. The curve of gastric secretion seems dependent on the hydrogen ion concentration of the intestinal contents. Thus in experiments in which the intestinal p_H was 3.0 or higher the rate of secretion was similar to that of control experiments. When the p_H was only 2.5, the secretion was depressed 50 per cent; almost complete inhibition resulted when the p_H was 2.0 or lower. A 0.9 per cent hydrochloric acid solution infused into the duodenum had no inhibitory effect. Histamine secretion is apparently not affected by

58. Grossman, M. I.; Dutton, D. F., and Ivy, A. C.: An Attempt to Confirm the Alleged Inhibitory Effect on Gastric Secretion of Jejunal Pedicle Grafts in the Wall of the Stomach, *Surgery* **17**:685-692, 1945.

59. Thornton, T. F.; Storer, E. H., and Dragstedt, L. R.: Supra-Diaphragmatic Section of Vagus Nerves and Gastric Secretion in Patients with Peptic Ulcer, *Proc. Soc. Exper. Biol. & Med.* **59**:140-141, 1945.

60. Storer, E. H.; Thornton, T. F., Jr., and Dragstedt, L. R.: Supra-Diaphragmatic Section of the Vagus Nerves and Gastric Motility in Patients with Peptic Ulcer, *Proc. Soc. Exper. Biol. & Med.* **59**:141-142, 1945.

61. Babkin, B. P.; Schaghter, M., and Nisse, R.: Further Studies on the Relationship Between the Vagal Secretory Function and the Chemical Phase of Gastric Secretion, *Clinics* **3**:494-505, 1944.

this regulatory mechanism.⁶² Isotonic solutions of proteose, amino acids and sodium chloride failed to elicit secretion of gastric juice in fasting dogs when administered into the intestine in the absence of bile; bile alone was without effect; a moderate period of secretion was obtained after a latent period of one to two hours when proteose mixed with bile or hypertonic solution of amino acids or sodium chloride was placed in the intestine. Bile in the stomach stimulated secretion. Apparently the products of protein digestion alone do not elicit an intestinal phase of gastric secretion.⁶³

Necheles and Olson,⁶⁴ observing the "corrosion" or "digestion" of metal cannulas used in the gastric pouches of experimental animals, found that plating with various metals was of little value and that brass cannulas were the most resistant.

Roentgen irradiation of the gastric region in dogs produced only minor anatomic changes in the mucosa and a transitory moderate anemia of the secondary type followed by an erythrocytotic phase after the cessation of treatment. The chief cells are the most sensitive; the parietal cells are more resistant.⁶⁵

Hollander⁶⁶ points out that the mucus secreted in response to chemical irritation invariably contains large numbers of columnar epithelial cells with two or three other types, some of which may be goblet cells and may indicate the development of gastritis. It is suggested that these may be significant in cancer research.

Segal, Hodge, Watson and Scott⁶⁷ found that Amberlite IR-4, a polyamine-formaldehyde synthetic resin, produced elevation of the p_H of the gastric juice and inactivation of pepsin, the last action depending on the hydrogen ion concentration of the solution.

62. Pincus, I. J.; Friedman, M. H. F.; Thomas, J. E., and Reh fuss, M. E.: A Quantitative Study of the Inhibitory Effect of Acid in Gastric Secretion, *Am. J. Digest. Dis.* **11**:205-208, 1944.

63. Beamer, W. D.; Friedman, M. H. F.; Thomas, J. E., and Reh fuss, M. E.: Factors Responsible for the Intestinal Phase of Gastric Secretion, *Am. J. Physiol.* **141**:613-618, 1944.

64. Necheles, H., and Olson, W. H.: Note on the "Digestion" of Metal in the Stomach, *J. Lab. & Clin. Med.* **29**:687-689, 1944.

65. Hueper, W. C., and de Carvajal-Forero, J.: The Effects of Repeated Irradiation of the Gastric Region with Small Doses of Roentgen Rays upon the Stomach and Blood of Dogs, *Am. J. Roentgenol.* **52**:529-534, 1944.

66. Hollander, F.: Physiology of Mucus Secretion, *J. Nat. Cancer Inst.* **5**:367, 1945.

67. Segal, H. L.; Hodge, H.; Watson, J. S., and Scott, M. W. J.: A Polyanine-Formaldehyde Resin: I. Its Effect upon the p_H of Acidified Solutions and the p_H and Pepsin of Gastric Juice in Vitro; II. Its Toxicity in Rats; Preliminary Feeding Tests, *Gastroenterology* **4**:484-496, 1945.

Gastric Motility.—Brody and Quigley⁶⁸ describe a method of measuring the motility of the pyloric sphincter in the unanesthetized dog by means of electromagnetic coils. Chronic experiments can be carried out. Crohn, Olson and Necheles⁶⁹ found that anesthetic drugs applied topically to the mucosa inhibited intestinal motility and tone but not gastric motility. Menendez Feros⁷⁰ reports his experiences in the electrocardiographic testing of 112 patients. The hydrogen ion concentration of the intragastric electrolyte solution, the local changes of the gastric tissue and various other factors influence the graphs. The significance of this procedure cannot be determined at present.

Diaphragmatic Hernia.—The roentgenologic diagnosis of parasternal herniations is discussed.⁷¹ Unusual cases include a congenital diaphragmatic hernia in a 5½ week old boy surgically repaired.⁷² A 57 year old man with symptoms of acute obstruction was found at operation to have a diaphragmatic hernia with torsion, as well as complete inversion of the stomach with reversal of the position of the antrum and the duodenal cap, together with eventration of the diaphragm.⁷³

Diverticulum.—Five more cases of diverticulum of the stomach are reported; gastroscopy aided in the diagnosis in 3.⁷⁴

Congenital Pyloric Stenosis.—Vance⁷⁵ reports 27 cases in which congenital pyloric stenosis was treated by pyloromyotomy, with 1 death. In 95 per cent of the cases the pyloric tumor was felt in the right upper

68. Brody, D. A., and Quigley, J. P.: Application of the "Inductograph" to the Registration of Movements, Particularly of Body Structures Such as the Pyloric Sphincter, *J. Lab. & Clin. Med.* **29**:863-867, 1944.

69. Crohn, N.; Olson, W. H., and Necheles, H.: The Local Effect of Topic Anesthetic Drugs on the Motility of the Gastrointestinal Tract of the Human and the Dog, *Surg., Gynec. & Obst.* **79**:41-49, 1944.

70. Menendez Feros, J.: Study on the Electro-Cardiographic Test: Its Possibilities in Differentiating Benign or Malignant Gastric Changes, *Rev. Gastroenterol.* **12**:99-110, 1945.

71. Ritvo, M., and Peterson, O. S., Jr.: Parasternal Diaphragmatic Hernia, *Am. J. Roentgenol.* **52**:399-405, 1944.

72. Wilson, A., and Trueman, K. R.: Repair of Congenital Diaphragmatic Hernia in an Infant, *Canad. M. A. J.* **52**:181-182, 1945.

73. Gardiner, H.: Diaphragmatic Hernia with Torsion of the Stomach and Acute Obstruction, *Brit. M. J.* **2**:114-115, 1944. Rosenfeld, D. H.: Unusual Type of Inversion of the Stomach Associated with Diaphragmatic Eventration and Other Anomalies, *Am. J. Roentgenol.* **52**:607-610, 1944.

74. Whitehouse, F., and MacMillan, J. M.: Gastric Diverticulum: Gastroscopic Observation of Two Cases, *Gastroenterology* **3**:13-22, 1944. Hunter, A. F.: Prepyloric Diverticulum of the Stomach Demonstrable Only by Pressure Roentgenograms, *Am. J. Roentgenol.* **52**:595-597, 1944. Frank, L. L.: Diverticulum of the Stomach: Case Report, *ibid.* **52**:510-513, 1944.

75. Vance, C. A.: Congenital Pyloric Stenosis, *Tr. South. S. A.* (1943) **55**:63-73, 1944.

quadrant, a little above the level of the umbilicus, at the outer border of the right rectus muscle. Dehydration was a prominent sign.

Gastroscope and Gastritis.—Hardt⁷⁶ describes the advantage obtained by using a flexirigid gastroscope that gives an angle of visualization of 80 degrees without shifting of the instrument and an image approximately two and a half times as large as that with the flexible gastroscope. The instrument reduces the size of the blind areas in the stomach and causes the patient less discomfort. Hufford and Stonehouse⁷⁷ found that the greatest degree of flexion of the gastroscope occurs in the esophagus (10 degrees) and a lesser degree (5 degrees) in the fundus of the stomach. Whitehouse and MacMillan⁷⁸ suggest that the tip be colored green or some other identifiable color to prevent mistaking it for an ulcer.

Howard⁷⁹ in an excellent paper reviews his experience with the gastroscope and concludes that, while it rarely reveals an ulcer or a tumor not demonstrated by roentgenogram, gastroscopy is nevertheless valuable for the objective demonstration of the coarser gastric lesions. Chronic gastritis is an interesting finding that usually is not of great clinical importance. In a critique of gastroscopy as employed in 1,730 patients with 2,200 examinations, Tanner⁸⁰ reports that of 631 gastric ulcers no fewer than 159 were diagnosed by gastroscopy alone, having been missed by expert radiologists.

Analysis of 191 gastroscopic examinations of 143 patients disclosed 25 cases of superficial gastritis, 21 of hypertrophic gastritis, 7 of atrophic gastritis, 5 of gastric ulcer, 6 of postoperative gastritis and 77 of normal stomachs.⁸¹ Tavares,⁸² studying 100 consecutive pre-Pearl Harbor patients with dyspepsia, found that in the group with duodenal ulcer (24 patients) the gastric mucosa was normal in 12 and gastritis was present in 11. In his study of 14 patients with unexplained gross hemorrhage and no roentgenographic evidence, he found no gastric

76. Hardt, L. L.: The Flexi-Rigid Gastroscope, *Gastroenterology* **3**:508-511, 1944.

77. Hufford, A. R., and Stonehouse, G. G.: Orientation of the Gastroscope by Roentgenograms, *Am. J. Digest. Dis.* **12**:61-64, 1945.

78. Whitehouse, F. R., and MacMillan, J. M.: Visualization of Rubber Tip of Gastroscope: Differentiation from Gastric Ulcer, *Gastroenterology* **3**:103-105, 1944.

79. Howard, J. T.: Experiences with the Gastroscope over a Period of Six Years, *South. M. J.* **38**:293-302, 1944.

80. Tanner, N. C.: A Critique of Gastroscopy, *Brit. M. J.* **2**:849-851, 1944.

81. Loe, R. H., and Berger, E. H.: Gastric Diseases in Navy Personnel: A Study of One Hundred Ninety-One Gastroscopic Examinations, *U. S. Nav. M. Bull.* **43**:450-458, 1944.

82. Tavares, C. A.: Review of Gastroscopic Studies on One Hundred Consecutive Pre-Pearl Harbor Military Patients, *War Med.* **7**:304-308 (May) 1945.

lesion in 2, superficial gastritis in 6, atrophic gastritis in 1 and gastric ulcer in 2; in 3 the examinations were unsatisfactory.

Of 54 patients with benign gastric ulcer, 74 per cent had associated gastritis: superficial in 26 (48 per cent), hypertrophic in 6 (11 per cent), atrophic in 7 (13 per cent) and combined atrophic and superficial in 1 (2 per cent).⁸³

Of 29 patients with pyloric obstruction due to duodenal ulcer, gastroscopic evidence of gastritis was found in 86 per cent, as compared with 62 per cent of patients without pyloric obstruction. Severe gastritis was noted six times as frequently in the group with stasis. Hence it is concluded that retention of gastric contents is associated with inflammatory change in the mucosa.⁸⁴

Crohn⁸⁵ in discussing the present status of gastritis emphasizes the possible relation of antral gastritis to carcinoma. Vaughan⁸⁶ presents a roentgenologic and gastroscopic study of 3 cases in which this condition simulated carcinoma, describing his findings in detail. Hinkel⁸⁷ reports a case in which localized hypertrophic gastritis of the cardiac portion simulated benign tumor; Harris,⁸⁸ an instance of hypertrophic gastritis simulating carcinoma roentgenologically.

Bennett⁸⁹ in opening a discussion of gastritis points out that at the present time the diagnosis must rest principally on gastroscopy and that in his experience there is no recognizable symptom complex. Jones suggests "that superficial, hypertrophic and atrophic changes can be stages and phases of a single disease process—a nonspecific gastritis." Of 337 patients admitted for hematemesis and melena, about half were examined by gastroscopy, usually in the first week; only in 7 instances were these findings attributed to acute gastritis. Twenty-five per cent of 553 new patients with peptic ulcer and 158 with dyspepsia but without roentgenographic evidence of ulcer were examined by gastroscopy; in 10 of this group severe gastritis was thought compatible with the clinical symptoms. Hancock stresses the importance of experience in

83. Horner, J. L., and Scheff, H.: Incidence of Gastritis in Gastric Ulcer, *Am. J. Digest. Dis.* **12**:202, 1945.

84. Scheff, H.; Horner, J. L., and Kenamore, B.: Gastroscopic Observations in Pyloric Obstruction, *Gastroenterology* **3**:506-507, 1944.

85. Crohn, B. B.: Newer Advances in Our Knowledge of Gastritis, *J. Mt. Sinai Hosp.* **11**:75-82, 1945.

86. Vaughan, W. W.: Antral Gastritis: Roentgenologic and Gastroscopic Findings, *Radiology* **44**:531-542, 1945.

87. Hinkel, C. L.: Hypertrophic Gastritis Simulating Intramural Tumor of the Stomach, *Am. J. Roentgenol.* **53**:20-27, 1945.

88. Harris, C. M.: Hypertrophic Gastritis Simulating Carcinoma, *Am. J. Surg.* **68**:261-265, 1945.

89. Bennett, T. I.; Jones, F. A.; Hancock, P. E. T.; Gill, M., and Tanner, N. C., in Discussion on Gastritis, *Proc. Roy. Soc. Med.* **38**:81-90, 1944.

the diagnosis of hypertrophic gastritis, observing that in 1,400 gastroscopic examinations hypertrophic changes were diagnosed in 6 per cent of the first 300 and in only 0.66 per cent of the last 300. Normal areae gastricae may easily be interpreted as hypertrophic gastritis. Gill, examining the stomach after administration of histamine (effect on the mucosa) and insulin (effect on the nervous mechanism), found that in the normal stomach the mucosa becomes hyperemic and exudes a clear fluid which "trickles downward" in rivulets between the folds to form a pool on the greater curvature. The secretion rate averages 2.5 to 3.5 cc. per minute and the hydrochloric acid from 100 to 120 cc. In stomachs with hypertrophic gastritis the highest concentration of free hydrochloric acid was 160 to 200 cc., and the highest rate of secretion was 6 to 6.5 cc. per minute. This suggests that some forms of hypertrophic gastritis are accompanied by, or indeed perhaps merely represent, physiologic hyperactivity of the mucosa. In stomachs with atrophic gastritis there is pallor with diminution of secretory function, the rate of secretion being less than 1 cc. per minute. These findings suggest a degenerative process, although certainly in some cases regeneration with return of function can occur to some degree spontaneously. Gill suggests the terms "mucosal hypertrophy," "mucosal atrophy" and "mucosal hyperemia." Tanner considers that polypoid hyperplasia may be simulated by edema and congestion secondary to gastric stasis associated with duodenal ulcer. Of 1,730 patients with 2,200 gastroscopic examinations, only 4 per cent had gastritis of a severity considered compatible with clinical symptoms; 631 gastric ulcers were noted in the group.

Phlegmonous Gastritis.—Four cases of phlegmonous gastritis were encountered in 4,007 autopsies. The diagnosis was not made clinically. The disease is apparently a manifestation of sepsis with the agent localizing in the wall of the stomach rather than invading locally from the lumen.⁹⁰

Corrosive Gastritis.—Meyer and Steigmann⁹¹ report 4 cases of corrosive gastritis complicated by pyloric obstruction and point out that alkaline corrosives usually affect the esophagus, whereas acid corrosives most frequently result in pyloric obstruction. Three premature infants fed a milk mixture containing an excess of lactic acid died from acute hemorrhagic and gangrenous gastritis.⁹²

90. Sachs, L. J., and Angrist, A.: Phlegmonous Gastritis as a Manifestation of Sepsis, *Ann. Int. Med.* **22**:563-584, 1945.

91. Meyer, K. A., and Steigmann, F.: The Surgical Treatment of Corrosive Gastritis, *Surg., Gynec. & Obst.* **79**:306-310, 1944.

92. Young, E. G., and Smith, R. P.: Lactic Acid: A Corrosive Poison; Report of Three Fatal Cases with Experimental Confirmation, *J. A. M. A.* **125**: 1179-1181 (Aug. 26) 1944.

Syphilis.—Voss⁹³ reports another instance of gastric syphilis thought clinically and at operation to be carcinoma. Gore and McCarthy⁹⁴ describe a 26 year old soldier with epigastric pain of one and a half year's duration, achlorhydria, serologic evidence of syphilis and a persistent prepyloric defect not appreciably influenced by four weeks of antisyphilitic therapy. After partial gastric resection the lesion was found to consist of a shallow mucosal ulceration with marked edema of the submucosa, thickening of the gastric wall, endarteritis, perivascular infiltration and nodular aggregates of epithelial cells unassociated with caseation or necrosis; giant cells were rare. The total picture, including the lack of endophlebitis, led the authors to reject the diagnosis of gastric syphilis in preference for localized Boeck's sarcoid. [To the reviewers the diagnosis of gastric syphilis seems much more probable.]

Aneurysm.—Taylor⁹⁵ reports a case of an anastomotic aneurysm of the left and right gastric arteries with rupture and fatal intraperitoneal hemorrhage.

Surgical Treatment.—In experiments performed on dogs, living omental patches satisfactorily sealed defects artificially produced in the stomach, whereas free grafts were susceptible to infection and the corrosive action of the digestive juice.⁹⁶

The distress which is not infrequently felt in the upper abdominal area after partial or subtotal gastrectomy tends to decrease and disappear after the first postoperative year, as the stomach becomes adjusted to smaller meals and jejunal reservoirs are formed, according to Ingelfinger.⁹⁷ The importance of hypoproteinemia in retarding postoperative gastric evacuation has been stressed, but there is no direct correlation between the level of serum protein and the rate of gastric emptying. The poor evacuation is not due so much to an abnormal stoma as to a flattened or reversed gastroenteric pressure gradient. Fats, hypertonic solutions and hydrochloric acid entering the intestinal loops distal to the anastomosis delay emptying in the resected as well as in the normal stomach by relaxation of the gastric musculature and not by sphincteric contraction. In patients with gastrectomy the absorption of protein and of carbohydrate is unchanged but that of fat may be slightly impaired.

93. Voss, F. H.: *Syphilis of the Stomach: A Case Report*, Rev. Gastroenterol. **12**:111-117, 1945.

94. Gore, I., and McCarthy, A. M.: *Boeck's Sarcoid: Report of a Case Involving the Stomach*, Surgery **16**:865-873, 1944.

95. Taylor, C. E.: *Ruptured Anastomotic Aneurysm of Gastric Arteries: Case Report and Review of Literature*, Am. J. Surg. **68**:258-268, 1945.

96. Price, P. B., and Lee, T. F.: *Use of Omentum to Close Perforations of the Stomach*, Arch. Surg. **50**:171-173 (March) 1945.

97. Ingelfinger, F. J.: *The Late Effects of Total and Subtotal Gastrectomy*, New England J. Med. **231**:321-327, 1944.

Bonorino and Castex⁹⁸ report that in a series of 43 gastrectomized patients they found roentgenologic evidence of decalcification in the pelvis and the spine in 39: slight in 7, moderate in 17, definite in 12 and conspicuous in 3. In the last group all the patients were over 60 years of age.

Benign Tumors.—The following interesting benign tumors have been described: an inflammatory cyst; an apple-sized solitary neurofibroma with a short broad pedicle; an enormous gastric schwannoma, which was surgically removed; a myoma with cancerous degeneration and ulceration; a benign myoma; a cancerous myoma with ulceration; a fibromyoma, and a papilloma.⁹⁹ Meissner¹⁰⁰ in an examination of 50 stomachs selected at random found 23 leiomyomas (46 per cent); they were not considered to be clinically significant.

Gastric Cancer.—(a) Incidence: Engel¹⁰¹ notes that there are about 38,000 deaths annually from cancer of the stomach in the United States. There are 150,000 to 170,000 deaths annually from cancer in the Union of Soviet Socialist Republics, 30 to 40 per cent being due to gastric cancer.¹⁰² Thorstad¹⁰³ observed no significant annual increase in the number of patients admitted because of gastric cancer in either the Harper Hospital or the City of Detroit Receiving Hospital. This is surprising, for the average age of the population continues to rise and the incidence of cancer increases with age.

(b) Genesis: Kirby¹⁰⁴ found no evidence of a significant lesion or tumor of the stomach in rats fed cholesterol heated to 300 C. for half an hour in amounts of 25 mg. per day for fifteen months, thus failing to confirm the assertion of Roffo.

98. Bonorino Udaondo, C., and Castex, M. R.: *Gastrectomía y descalcificación esquelética*, Prensa méd. argent. **32**:3-18, 1945.

99. Horan, M. J., Jr., and Comfort, M. W.: *Inflammatory Cyst of the Stomach Secondary to Cholecystic Disease: Report of Case*, Proc. Staff Meet., Mayo Clin. **20**:237-241, 1945. Sanguily, J., and Leon Blanco, F.: *Gastric Schwannoma: Report of a Large Intragastic Lesion Simulating a Bezoar*, Surgery **17**:328-336, 1945. Aksel, A.: *Solitary Neurofibroma in the Stomach*, Brit. M. J. **2**:309, 1944. Dewey, E. B.: *Benign Tumors of the Stomach*, Am. J. Surg. **65**:233-237, 1944.

100. Meissner, W. A.: *Leiomyoma of the Stomach*, Arch. Path. **38**:207-209 (Oct.) 1944.

101. Engel, G. C.: *Carcinoma of the Stomach and Its Problems*, Clinics **4**: 13-26, 1945.

102. Bocharov, A. A.: *Cancer of the Stomach*, Am. Rev. Soviet Med. **1**:532-539, 1944.

103. Thorstad, M. J.: *The Outlook on Carcinoma of the Stomach*, Am. J. Surg. **64**:242-247, 1944.

104. Kirby, A. H. M.: *Attempts to Induce Stomach Tumors: IV. The Effects of Cholesteryl Esters Heated to 300° C., and Cholesterol Heated to 430° C.*, Cancer Research **5**:129-134, 1945.

Strong¹⁰⁵ developed a strain of inbred mice in which methylcholanthrene produced tumors of diverse types. The descendants of these mice continued to show spontaneous development of gastric carcinoma. In the discussion of this tremendously important contribution the authors develop the concept "that the action of methylcholanthrene on the production of malignant lesions may be of a twofold nature: (1) the conversion of gastric mucosa into cancer; and (2) the production of a germinal mutation in a genetic entity which in some manner or other underlies certain morphologic or physiologic characteristics of gastric mucosa." The genetic aspect of this "inheritance of acquired characters" is well discussed by Jones, Little, Burns and Andervont.

Ivy¹⁰⁶ in an excellent and extensive review discusses the relations of gastric function and gastric cancer. The desirability of producing experimental chronic gastritis in animals is emphasized; the need for further study of the chemistry of mucus and its metabolism is pointed out, and numerous other facets of the problem of gastric cancer are noted. The paper should be read by all those interested in the subject. The discussion following it is likewise excellent. Stewart expresses the opinion that in general the concept that common chronic inflammatory lesions are involved in the causation of cancer is one from which pathologists have begun to steer away. Stout presents evidence to show that gastric cancer is more likely to develop in a stomach which shows atrophic changes in the presence of intestinal metaplasia, but he concludes that "whether these atrophic changes or the intestinal metaplasia have anything to do with the development of gastric cancer doesn't seem to me to have been proved at all." Stout did not find stages between metaplasia and the development of cancer. Warren expresses the opinion that "the significant type of chronic gastritis with respect to carcinoma is that in which there is epithelial alteration as well as purely inflammatory infiltration." Harvey and Stout refer to an interesting patient who underwent resection for a well differentiated fungating carcinoma and who twenty odd years later had a poorly differentiated and widely infiltrating tumor. Stewart hazards the wager that the greater the number of five year survivals, the more instances of this sort there will be. Warren and Meissner¹⁰⁷ present evidence to support the view that in chronic gastritis the exudative changes are not sig-

105. Strong, L. C.: Genetic Analysis of the Induction of Tumors by Methylcholanthrene: IX. Induced and Spontaneous Adenocarcinomas of the Stomach in Mice, *J. Nat. Cancer Inst.* 5:339-362, 1945.

106. Ivy, A. C.: Gastric Physiology in Relation to Gastric Cancer, *J. Nat. Cancer Inst.* 5:313-337, 1945.

107. Warren, S., and Meissner, W. A.: Chronic Gastritis and Carcinoma of the Stomach, *Gastroenterology* 3:251-256, 1944.

nificant but that the epithelial changes when severe may be comparable to well recognized precancerous lesions occurring elsewhere in the body.

Stout¹⁰⁸ examined, by the multiple section method, 50 stomachs with carcinoma, 50 with gastric ulcer and 50 with duodenal ulcer. Mucosal atrophy was found in a larger number and tended to be more widespread in the stomachs with cancer. When there was juxtaposition of carcinoma and mucosal gland, it was impossible to tell whether the carcinoma was invading the gland or developing from the epithelial cells of the gland.

. . . in occasional stomachs with carcinomas in them, multiple sections from various areas failed to show any epithelial changes at all in some while others showed only minimal changes. . . .

It would seem, therefore, that while atrophy of the gastric mucosal epithelium and cyst formation are present to a greater degree and in larger numbers in stomachs with carcinomas than in comparable stomachs without cancer, the exact relationship between these two conditions remains undetermined.

Pertinent to this discussion is the observation that, of 43,021 consecutive autopsies, 293 were performed on persons over 45 years of age who had pernicious anemia and that in 36 of these gastric cancer was present, an incidence of 12.3 per cent, three times that of gastric carcinoma in persons of the same age group who did not have pernicious anemia.¹⁰⁹ In a roentgenologic study of 211 patients with pernicious anemia 17 (8.0 per cent) were found to have carcinoma and 15 (7.1 per cent) benign tumors, a total of 32, or 15.1 per cent. These observations constitute further evidence of an etiologic rather than an accidental relationship between pernicious anemia and gastric epithelial tumors.¹¹⁰

(c) Pathologic Aspects: Stout¹¹¹ calls attention to the carcinomas in which extension is chiefly centrifugal, the cells spreading along the plane of the gastric wall.

. . . Grossly, these tumors thicken the mucosa and obliterate its folds, usually with shallow, bowl-shaped ulceration, or else they spread outward from the margins of a deep peptic ulcer . . . the regional-node metastatic rate in the group of 23 patients studied at the Presbyterian Hospital was only 39 per cent as compared with 75

108. Stout, A. P.: Gastric Mucosal Atrophy and Carcinoma of the Stomach, *New York State J. Med.* **45**:973-977, 1945.

109. Kaplan, H. S., and Rigler, L. G.: Pernicious Anemia and Carcinoma of the Stomach: Autopsy Studies Concerning Their Interrelationship, *Am. J. M. Sc.* **209**:339-348, 1945.

110. Rigler, L. G.; Kaplan, H. S., and Fink, D. L.: Pernicious Anemia and the Early Diagnosis of Tumors of the Stomach, *J. A. M. A.* **128**:426-432 (June 9) 1945.

111. Stout, A. P.: Superficial Spreading Type of Carcinoma of the Stomach, *J. Nat. Cancer Inst.* **5**:363, 1945.

per cent for the 123 gastric carcinomas resected during the same period. . . . there is reason to anticipate a 5-year cure rate of at least 50 per cent. Thus the superficial spreading carcinoma is one of the more curable forms of gastric cancer.

In necropsies of 243 persons with gastric cancer it was found that 9 per cent had multiple cancerous tumors; this is slightly higher than the general level, of 6.8 per cent. In necropsies of 476 persons with carcinoma of the large intestine the incidence of multiple cancerous lesions was 15 per cent.¹¹² A 60 year old man with coexistent primary carcinomas in the stomach and the rectosigmoid underwent successfully a double resection of the segments involved in spite of pulmonary tuberculosis.¹¹³

A primary carcinoma of the stomach produced a spontaneous gastrocolic fistula.¹¹⁴ Metastatic involvement of the umbilicus in inoperable carcinoma has again been described.¹¹⁵ In 1 case a diffuse lymphatic spread with metastases in the lungs and bone marrow gave an unusual roentgenogram of the chest and an eosinophilia of 27 per cent, creating a difficult diagnostic problem.¹¹⁶

Lowman and Kushlan¹¹⁷ emphasize the importance of a careful pelvic examination of any female patient with intestinal symptoms, because of the incidence of ovarian metastases. The roentgenologic demonstration of an irritation of the small bowel may suggest the presence of generalized peritoneal carcinomatosis.

(d) Ulceration, Healing and Growth: Tumor tissue is exposed to peptic ulceration in the stomach only. Certain ulcerating gastric carcinomas may present the structure characteristic of peptic ulcer. This typical structure is attributed to peptic digestion of the carcinoma and adjacent tissue. In such ulcers there may be marked or even complete repair of the tissue defect. The scar of the ulcer may be covered by neoplastic mucosa or by a layer of epithelium perfectly normal in appearance. The disappearance of the ulcer crater as seen by roentgenogram does not prove, therefore, that the ulcer is of a benign nature. Likewise, the demonstration of neoplasm in one edge of an ulcer does not prove it to have been a benign ulcer with cancerous

112. Warren, S.: Multiple Cancers of the Human Gastrointestinal Tract, *J. Nat. Cancer. Inst.* **5**:375, 1945.

113. Pemberton, J. D., and Seefeld, P. H.: Simultaneous Primary Carcinomas of the Stomach and Sigmoid, *Am. J. Surg.* **66**:393-395, 1944.

114. Shirley, A. R.: An Unusual Gastrocolic Communication, *Radiology* **43**:588-590, 1944.

115. Lombardi, L. E., and Parsons, L.: Carcinoma of the Umbilicus Metastatic from Carcinoma of the Stomach, *Ann. Int. Med.* **22**:290-293, 1945.

116. Cabot Case 31242, *New England J. Med.* **232**:708-713, 1945.

117. Lowman, R. M., and Kushlan, S. D.: "The Krukenberg Tumors": The Roentgen and Gastroenterological Aspect of Secondary Ovarian Carcinoma, *Gastroenterology* **4**:305-322, 1945.

degeneration. Peptic ulceration and healing in primary carcinoma may well account for both phenomena. Eusterman, Fitzgibbon and Crohn present corroborative evidence.¹¹⁸

Of interest in this connection, and again illustrating the fact that in a case of gastric cancer a long history may not be indicative of so-called carcinomatous degeneration of a benign ulcer, is the reporting once more of a patient with a gastroenterostomy for duodenal ulcer in whom ten years later an independent cancer developed at the stoma.¹¹⁹

Schwartz¹²⁰ describes an exceedingly interesting case of a slow-growing carcinoma with which anemia was associated in consequence of its having metastasized to the bone marrow, as proved by biopsy. In spite of this, the patient, aided by blood transfusions, survived for three years. The gastric lesion, a small ulcerating carcinoma, was not found by roentgenographic or gastroscopic examination but was demonstrated at autopsy, near the cardia. Diffuse metastatic lesions were found in the liver and the bone marrow.

(e) Anemia: Of 122 patients with gastric cancer, 78 were found to have anemia: In 25 the anemia was macrocytic; in 35, normocytic, and in 18, microcytic; in most instances the anemia was normochromic.¹²¹

(f) Surgical Treatment: Of 143 patients with carcinoma of the stomach who died without surgical treatment, the lesion was confined to the stomach in 10 per cent and was theoretically curable by resection in 18 per cent.¹²² Brunschwig¹²³ points out the feasibility and the advisability of extensive and widespread resection of perigastric tissues in an effort to reduce the metastatic spread of small early carcinomas.

In 323 patients subjected to operation at the Mayo Clinic there were 16 deaths, a hospital mortality rate of 5 per cent. Sixty per cent of all the patients whose condition was diagnosed as gastric cancer underwent operation. In 58 per cent of these the lesion was resected. The ratio of resections to the total number of patients was

118. Palmer, W. L., and Humphreys, E. M.: Gastric Carcinoma: Observations on Peptic Ulceration and Healing, *Gastroenterology* **3**:257-272, 1944.

119. Gonzales Rodriguez, A., and d'Alotto, V.: Cáncer de una neoboca en una gastroenterostomia por ulcus duodenal, *An. Dispen. púb. nac. para enferm. d. ap. digest.* **7**:117-125, 1944; *Prensa méd. argent.* **31**:1883-1886, 1944.

120. Schwartz, S. O.: Longevity with Metastatic Carcinoma of the Stomach, *Ann. Int. Med.* **22**:727-730, 1945.

121. Oppenheim, A.; Abels, J. C.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract, *J. A. M. A.* **127**: 273-276 (Feb. 3) 1945.

122. Metheny, D.: Modern Trends in Gastric Surgery Through 1943, *West. J. Surg.* **52**:476-480, 1945.

123. Brunschwig, A.: Radical Surgery for Gastric Cancer, *J. Nat. Cancer Inst.* **5**:365-366, 1945.

35 per cent, about 9 per cent higher than three years ago. There were 164 partial gastrectomies, with a mortality of 4.9 per cent; 17 total gastrectomies, with a mortality of 29.4 per cent; 25 palliative operations, with a mortality of 8 per cent, and 117 explorations, with a mortality of 0.9 per cent.¹²⁴ In Engel's series¹²⁵ 21 per cent were hopeless when first seen by the surgeon; an exploratory laparotomy alone was performed in 42 per cent; palliative gastroenterostomy was carried out in 20 per cent; radical operation was possible in only 17 per cent. The mortality for subtotal gastrectomies is reported as 3 to 5 per cent and that for total gastrectomies as 18 to 25 per cent.

According to Bocharov,¹²⁶ more than 50 per cent of the patients with gastric cancer admitted to the Central Oncological Institute in Russia from 1925 to 1934 were found incurable. Between 1932 and 1936 only 12.2 per cent of the patients admitted had operable lesions. In 767 subjected to laparotomy 294 resections were carried out. Of the total of 916 patients with gastric cancer, 21.7 per cent had been ill for less than three months. In this group only 31.6 per cent (of the 21.7 per cent) were candidates for radical surgical intervention. Twenty-five per cent of the group had had symptoms for three years or more. Fifty per cent of this group were subjected to radical surgical treatment. Of the 916 patients, 99 (about 11 per cent) had had symptoms of over ten years' duration. Neoplastic degeneration of benign ulcer was considered to have been responsible for 16.3 per cent of 1,020 cases of gastric carcinoma. No such degeneration of duodenal ulcer was noted in 2,376 operations for gastric ulcer and 820 operations for gastric carcinoma. Resection was feasible in only 30 per cent of the patients with carcinoma of the lesser curvature and in only 10 per cent of those with tumor of the cardia. Surgical intervention was most effective in the age group between 20 and 50. Of the 916 patients subjected to operation, radical surgical removal was possible in only 349 (38.1 per cent), with a mortality rate of 32 per cent—cachexia, pneumonia and peritonitis being the most frequent causes of death. In 164 patients with uncomplicated resections the mortality rate was 12 per cent. In 144 patients whose cases were complicated by metastases palliative resection was carried out, with a mortality rate of 43 per cent. In a third group, consisting of 53 patients in whom partial

124. Counseller, V. S.; Waugh, M., and Clagett, O. T.: Report of Surgery of the Stomach and Duodenum for 1943, Proc. Staff Meet., Mayo Clin. **19**:586-592, 1944.

125. Engel, G. C.: Carcinoma of the Stomach and Its Problems, Clinics **4**:13-26, 1945.

126. Bocharov, A. A.: Cancer of the Stomach, Am. Rev. Soviet Med. **1**: 532-539, 1944.

resection of the colon was done in addition to total or subtotal gastrectomy, the mortality rate was 66 per cent. One hundred and eighteen patients were followed from one to ten years. There were 13 five year and 5 ten year cures after palliative resection. Of the total group, 84.9 per cent died within two years, and only 7.2 per cent survived five years.

The proportion of patients with clinically inoperable cancer of the stomach was 42.3 per cent at the Harper Hospital and 76.6 per cent at the City of Detroit Receiving Hospital. Fifty-seven per cent of all patients with gastric cancer admitted to Harper Hospital were subjected to surgical treatment, in contrast with only 23.4 per cent at the City of Detroit Receiving Hospital. At Harper Hospital gastroenterostomy was performed in 10.8 per cent of the entire series of patients, while at the City of Detroit Receiving Hospital only 3.7 per cent were treated thus. Gastrectomy was performed in 19.4 per cent of the patients at Harper Hospital and in 9.8 per cent of those at the Receiving Hospital. The mortality rate for gastrectomy at Harper Hospital during 1941 and 1942 was 29.0 per cent—a definite improvement over other years. Finally, no evidence was found to indicate that there had been a marked improvement in either diagnosis or treatment of early carcinoma of the stomach during this fifteen year period. It is assumed that these contrasting figures reflect the fact that the Harper Hospital is a private institution and the City of Detroit Receiving Hospital a municipal one. The private patients report to the physician earlier than do the indigent; thus an earlier diagnosis is made, more patients are subjected to laparotomy and more resections are possible. One wonders, however, if this is the complete explanation.¹²⁷

Custer¹²⁸ reports the follow-up of 96 patients with gastric cancer which was considered operable in a group of 141: Two died during operation (2.03 per cent); 9 died of fatal postoperative complications (9.37 per cent); 23 did not survive over three years (35.34 per cent); 36 (37.59 per cent) died in the three to five year interval; 26 survived five years (27.06 per cent); 18 were alive after eight years (18.75 per cent). In contrast with this, 28 patients who refused operation were all dead in three years. Lund¹²⁹ reports a partial gastrectomy performed in 1909 which the patient survived for thirty-five years. Allen,

127. Thorstad, M. J.: The Outlook on Carcinoma of the Stomach, *Am. J. Surg.* **64**:242-247, 1944.

128. Custer, W. C.: Survival After Gastric Resection in Carcinoma of the Stomach, *Surgery* **17**: 510-511, 1945.

129. Lund, F. B.: Partial Gastrectomy for Carcinoma Thirty-Five Years Ago, *New England J. Med.* **232**: 562-564, 1945.

in discussing this paper, refers to Parsons' study showing a five year curability rate of about 20 per cent for gastric carcinoma.

Jones and Kehm¹³⁰ in a follow-up report of 8 consecutive total gastrectomies states that all the patients are living, with postoperative periods varying from six to eighteen months. Lahey and Marshall¹³¹ report 73 total gastric resections, with 24 (33 per cent) postoperative deaths. The abdominal approach is considered safer than the transpleural. Fourteen of the operative deaths were due to peritonitis and 10 to medical complications involving the heart and the lungs. In 23 survivors ultimately dying of recurrent disease the average postoperative duration of life was eighteen months. Twenty-six patients have had no recurrence for periods ranging from six months to six years. The mortality rate in 28 operations performed in the past two years was 18 per cent. Sweet¹³² reports that 127 patients with carcinoma of the stomach or the esophagus were operated on by the transthoracic approach from 1939 to November 1944 at the Massachusetts General Hospital. Of 85 in whom the stomach or the lower part of the esophagus and the cardia were involved, 24 were found to have inoperable lesions. Of 42 midesophageal carcinomas, 17 were inoperable; 25 were resected, but only 11 of the 25 allowed high intrathoracic esophagogastric anastomosis. Fourteen were subjected to the Torek operation (prior to 1944). Of the 42 midesophageal carcinomas, 59.5 per cent were resectable. Partial gastrectomy with low esophagogastric anastomosis was carried out in 43 patients; total gastrectomy was performed in 18; partial gastrectomy with a high esophagogastric anastomosis in 11. In these three groups the mortality rates were, respectively, 18.6, 38.9 and 27.3 per cent. For the entire series of 72 patients undergoing partial or total esophagogastric resection the mortality was 25 per cent. Additional cases are reported by others.¹³³

[To the reviewers these somewhat confusing statistics seem to indicate a trend toward earlier diagnosis and a higher incidence of partial and of total gastrectomy. In general, the mortality rates have

130. Jones, T. E., and Kehm, R. W.: Total Gastrectomy: Report of Eight Cases, *Surg., Gynec. & Obst.* **80**: 534-538, 1945.

131. Lahey, F. H., and Marshall, S. F.: Indications for, and Experiences with, Total Gastrectomy Based upon Seventy-Three Cases of Total Gastrectomy, *Tr. South. S. A.* (1943) **55**: 12-32, 1944.

132. Sweet, R. H.: Transthoracic Resection of the Esophagus and Stomach for Carcinoma: Analysis of the Postoperative Complications, Causes of Death and Late Results of Operation, *Ann. Surg.* **121**: 272-284, 1945.

133. Griswold, R. A.: Transthoracic Gastrectomy for Unusual Lesions of the Stomach, *Ann. Surg.* **121**: 600-619, 1945. Milanes, F.; Vega, T.; Morales, E.; Rodriguez, A., and Diaz, R. A.: Total Gastrectomy: Clinical and Physiopathological Study, *Gastroenterology* **3**: 380-387, 1944.

gradually decreased and the survival rates increased. On the basis of the present evidence, however, the outlook in the presence of gastric cancer is still discouraging. Many lives will be lengthened by early diagnosis and operation, but physicians will never be able to look on a surgical procedure as a "cure" for this disease. It seems evident that in the majority of patients metastases occur before the symptoms are sufficiently definite to arouse the attention of the patient and to induce him, regardless of his economic status, to consult a physician. The diagnostic problems are, as a rule, not great. The difficulty is in the nature of the disease, its tendency toward early spread and the inability of the surgeon to cope successfully with the metastases.]

(g) Acute Perforation: The incidence of perforation varies from 2.8 to 6.0 per cent. Bisgard and Overmiller,¹³⁴ in reporting a recovery, review the literature and find that in 115 cases the mortality following simple closure is 80 per cent.

(h) Hodgkin's Disease: Of 213 patients with Hodgkin's disease, 24 had primary gastrointestinal symptoms, and yet only 9 had lesions of the digestive tract. During the course of the disease, abdominal symptoms were also frequent but were not due to local involvement. In 6 of 174 cases the disease was primary in the digestive tract; indeed, it was confined almost entirely to this tract. The stomach was involved in 3, the cecum in 2 and the duodenum and the esophagus each in 1. Multiple involvement of the digestive tract was not observed. None of the lesions were suspected during life. In cases of sarcoma, on the other hand, multiple involvement of the gastrointestinal tract is common.¹³⁵

(i) Lymphosarcoma: Miller and Eusterman¹³⁶ describe a patient with Mikulicz's syndrome who presented a peculiar pulmonary and gastric involvement. The gastroscopic appearance of the latter was suggestive of lymphoma. Biopsy of a nodule in the right orbit disclosed lymphosarcoma of a low grade. All the lesions responded beautifully to roentgen therapy. This observation leads the authors to question the assumption that the process in Mikulicz's original case was benign and self limited.

134. Bisgard, J. D., and Overmiller, W.: Emergency Gastrectomy for Acute Perforation of Carcinoma of the Stomach with Diffuse Soiling of the Free Peritoneal Cavity, *Tr. Am. Surg. A.* **62**: 526-530, 1944; *Ann. Surg.* **120**: 526-530, 1944.

135. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's Disease: IV. Involvement of Certain Organs, *New England J. Med.* **232**: 547-559, 1945.

136. Miller, J. R., and Eusterman, G. B.: Mikulicz's Syndrome: Report of a Case with Associated Pulmonary and Gastric Lesions, *Proc. Staff Meet., Mayo Clin.* **19**: 425-431, 1945.

Rafsky, Katz and Krieger,¹³⁷ reporting 11 cases of lymphosarcoma of the stomach, proved to be such, and another, probable case, failed to find any characteristic history. In 50 per cent there was a history simulating that of peptic ulcer. In 33 per cent the physical examination revealed an abdominal mass; in 33 per cent the correct diagnosis was made by roentgenogram; in 50 per cent the lesion simulated carcinoma. The gastric acidity varied widely. The gastroscopic appearance of the 4 stomachs examined was not characteristic of cancerous involvement: There was striking hypertrophy of the mucosal folds; the mucous membrane appeared swollen and edematous, but it was intact; later in the disease flattened ulcerated areas were seen on the crests of the folds. The diagnostic difficulties in such cases are further illustrated by a lesion not seen roentgenologically and not positively identified gastroscopically because of the similarity of carcinoma, lymphoma and gastritis. Subtotal gastrectomy was performed. The authors suggest, however, that in the case of an inoperable gastric tumor radiation therapy may be indicated in the hope that the lesion may be a radiosensitive lymphoma.¹³⁸ A lymphosarcoma with metastases and chyloform ascites is reported.¹³⁹

Peptic Ulcer.—(a) Incidence: Morris and Titmuss,¹⁴⁰ in analyzing the mortality from peptic ulcer as revealed in the reports of the Registrar General for England and Wales, found that in men the mortality is steadily rising, the process having been accelerated in the period from 1939 to 1941, whereas in women the mortality has been falling except for a slight reversal of the trend in the period from 1939 to 1941. The important increase in the death rate of both gastric and duodenal ulcer is in men over 45. The mortality from gastric ulcer is heavier than that from duodenal ulcer, the pattern resembling that of gastric cancer. The mortality is higher in the Greater London areas and lowest in the rural sections. There is no significant class bias, although in old age deaths are heavier among the well-to-do. The authors find it "hard to resist the conclusion that urban life nowadays is an ideal soil for the flowering of the ulcer temperament." Carslaw,¹⁴¹ in Glasgow,

137. Rafsky, H. A.; Katz, H., and Krieger, C. I.: Varied Clinical Manifestations of Lymphosarcoma of the Stomach, *Gastroenterology* 3: 297-305, 1944.

138. Paul, W. D., and Parkin, G. L.: Lymphosarcoma of the Stomach: A Gastroscopic Report, *Gastroenterology* 3: 214-217, 1944.

139. Martin, L.; Pereira Torres, R. A., and Lazzar, A.: Linfosarcomatosis gástrica, *Prensa méd. argent.* 32:474-475, 1945.

140. Morris, J. N., and Titmuss, R. M.: Epidemiology of Peptic Ulcer: Vital Statistics, *Lancet* 2: 841-845, 1944.

141. Carslaw, J.: A Study of the Number of Cases Treated in the Western Infirmary of Glasgow During Forty-Six Years (1897 to 1942), *Glasgow M. J.* 24: 183-188, 1944.

found over a period of forty-five years an "appalling increase" in duodenal ulcer, both perforated and unperforated, especially in men.

The incidence of acute perforation during a twenty year period (1924 to 1943) in West Scotland increased progressively up to 1938, rose impressively in 1940-1941 and then decreased. The 1940-1941 rise was not correlated with air raids. The authors suggest that, in addition to anxiety about the war situation, overwork and perhaps undernutrition may have exerted an influence. The sex ratio underwent little variation. The lesion was rare in childhood, rose infrequently in adolescence and attained a maximum between the ages of 30 and 40 years. Perforations were uncommon in August, September and October and common in December. They were less frequent on Sundays and Mondays and were unduly common between 3 p.m. and 6 p.m.¹⁴²

(b) Etiologic Factors: Herbut¹⁴³ reports that in 5 patients acute peptic ulcer developed after distant operations, but no evidence is presented to indicate a casual relationship.

Koch and Fischer¹⁴⁴ describe a patient who twenty-three days after a severe burn of the leg died from perforation of an acute ulcer of the duodenum.

Gray¹⁴⁵ describes 29 patients in whom trauma apparently resulted in the formation of a peptic ulcer.

(c) Experimental Observations: The incidence of gastrojejunal ulcer in dogs with complete intragastric regurgitation of the contents of the duodenal loop is dependent on the length of the afferent duodenojejunal loop, since only 1 ulcer developed in 11 dogs with a short loop (8 to 15 cm.) and 5 in 6 dogs with a long loop. Four of these died of generalized peritonitis secondary to perforation.¹⁴⁶ In a study of gastric resection three series of experiments were carried out in 22 dogs. Eleven were subjected to a 75 per cent resection with a short (12 to 15 cm.) duodenal loop; in none did ulcer develop in response to stimulation with "histamine in beeswax." In the second series

142. Illingworth, C. F. W.; Scott, L. D. W., and Jamieson, R. A.: Acute Perforated Peptic Ulcer: Frequency and Incidence in the West of Scotland, *Brit. M. J.* **2**:617-620 and 655-658, 1944.

143. Herbut, P. A.: Acute Peptic Ulcers Following Distant Operations, *Surg., Gynec. & Obst.* **80**: 410-415, 1945.

144. Koch, V. W., and Fischer, W. A.: Duodenal Ulcer with Perforation Following a Cutaneous Burn: Report of a Case, *Ann. Int. Med.* **22**: 719-727, 1945.

145. Gray, I.: Trauma in Relation to Peptic Ulcer, *New York State J. Med.* **45**: 887-892, 1945.

146. Merendino, K. A.; Varco, R. L.; Litow, S.; Kolouch, F., Jr.; Baronofsky, I., and Wangenstein, O. H.: I. Stomal Ulcer Attending Complete Intragastric Regurgitation Influenced by Length of Afferent Duodenojejunal Loop, *Proc. Soc. Exper. Biol. & Med.* **58**:222-225, 1945.

(7 dogs) a long afferent duodenal loop was used (27 to 78 cm.); after histamine stimulation a gastrojejunal ulcer resulted in each animal. In the last series, 4 dogs with long afferent duodenojejunal loops received no histamine after gastric resection, but 2 showed, nevertheless, spontaneously developed, perforated gastrojejunal ulcers.¹⁴⁷ In 12 gastrojejunosomized dogs the incidence of ulcer varied according to the length of the duodenojejunal loop—from 16.2 per cent when the loop was short to 66.6 per cent when it was long.¹⁴⁸ Small gastric resections (25 to 50 per cent) when there is no afferent loop (Billroth's operation I) are accompanied by a high incidence of histamine-invoked ulcers, whereas when a three-quarter resection is done, stomal ulcer cannot be produced with histamine. These experiments all seem to emphasize in ulcer formation the ratio between the quantity of acid gastric juice and the quantity of neutralizing intestinal content, or the net peptic activity.¹⁴⁹

Driver, Chappell and Carmichael¹⁵⁰ studied the digestion of the mucosa in different portions of the jejunum in dogs, using varying concentrations of pepsin in tenth-normal hydrochloric acid, and found that "the more distal loops of the gut seemed to be more susceptible to the action of pepsin in hydrochloric acid than the more proximal segments." A rise in hydrostatic pressure resulted in an impressive increase in the extent of peptic digestion and a decrease in the time required for perforation. At 45 cm. pressure the average time for perforation was found to be three hundred minutes; at 90 cm. pressure, eighty-two minutes, and at 135 cm. pressure, only forty-one minutes.¹⁵¹

Conversely, the time required for perforation was lengthened by raising the intra-abdominal pressure. Under atmospheric pressure the interval of time was eighty-two minutes; with 20 cm. of saline solution it was increased to one hundred and sixteen minutes, and at 45 cm. pres-

147. Merendino, K. A.; Lannin, B. G.; Kolouch, F., Jr.; Baronofsky, I.; Litow, S. S., and Wangenstein, O. H.: Length of Afferent Duodenojejunal Loop in Gastric Resection: A Factor in Stomal Ulcer, *Proc. Soc. Exper. Biol. & Med.* **58**:226-230, 1945.

148. Kolouch, F., Jr.; Castellanos, M.; Dubus, A. T. S.; Baronofsky, I., and Wangenstein, O. H.: III. Mechanism of Stomal Ulcer Is Related to Length of Afferent Duodenojejunal Loop, *Proc. Soc. Exper. Biol. & Med.* **58**: 275-280, 1945.

149. Baronofsky, I.; Lannin, B. G.; Sanchez-Palomera, E., and Wangenstein, O. H.: Billroth I, Gastric Resection: Extent Necessary to Protect Against Histamine-Provoked Ulcer, *Proc. Soc. Exper. Biol. & Med.* **59**: 229-231, 1945.

150. Driver, R. L.; Chappell, R. H., and Carmichael, E. B.: Effect of Concentration of Pepsin and the Differential Susceptibility of Jejunal Segments in Experimental Jejunal Ulcers in the Dog, *Am. J. Digest. Dis.* **12**: 166-167, 1945.

151. Driver, R. L.; Chappell, R. H., and Carmichael, E. B.: Effect of Hydrostatic Pressure on the Experimental Production of Ulcers, *Am. J. Digest. Dis.* **12**: 168-169, 1945.

sure, to one hundred and eighty-five minutes.¹⁵² The proteolytic enzymes rennin, trypsin and erepsin under a hydrostatic pressure of 90 cm. of water produced necrosis, rennin being the most active of the three. The average time required to produce perforation with tenth-normal hydrochloric acid alone was about 50 per cent more than was required with rennin and tenth-normal hydrochloric acid. Neither steapsin nor amylolysin caused necrosis.¹⁵³

Nasio¹⁵⁴ found that "cinchophen ulcers" occur at an average of thirteen days after the administration of the drug has begun. During the first five days congestive-hemorrhagic gastroenteritis is present, followed by erosive gastritis, which diminishes when the peptic ulcer appears. The administration of 10 to 20 mg. of naphthoquinone did not prevent the production of ulcer, nor did 180,000 to 360,000 units of vitamin A.¹⁵⁵ Nicotinic acid seemed to favor ulcer formation and produced, when given alone, an inflammation of the gastrointestinal tract.¹⁵⁶

Typical peptic ulcers could be produced in 40 per cent of guinea pigs and cats by daily administration of 100 mg. of caffeine in beeswax. In pouch dogs the injection of 1,200 mg. of caffeine (alkaloid) in aqueous solution increased the acidity and the volume of secretion in two thirds of the experiments. A prolonged definite increase of secretion was observed in dogs given 2,500 mg. of caffeine (alkaloid) in beeswax for four consecutive days. In human subjects, 2 cups of black coffee increased gastric secretion in 73 per cent of the tests; caffeine and sodium benzoate U. S. P. (300 to 976 mg.) evoked a marked response in 90 per cent of the tests.¹⁵⁷ Roth and Ivy¹⁵⁸ present evidence that caffeine-

152. Chappell, R. H.; Driver, R. L., and Carnichael, E. B.: Increased Intra-Abdominal Pressure as a Means of Inhibiting Perforations Due to Pepsin Solutions Under Hydrostatic Pressure in the Small Intestines of Dogs, *Am. J. Digest. Dis.* **12**: 169-171, 1945.

153. Driver, R. L.: Ulcer Production in Intestines of Dogs by Various Enzymes Under Hydrostatic Pressure, *Proc. Soc. Exper. Biol. & Med.* **59**: 281-282, 1945.

154. Nasio, J.: La úlcera péptica experimental cincofénica: I. Producción y patología, *Prensa méd. argent.* **31**:2659-2669, 1944.

155. Nasio, J.: Acción de la vitamina K sobre la úlcera péptica cincofénica, *Prensa méd. argent.* **32**: 476-477, 1945; Acción de algunas vitaminas sobre la úlcera péptica cincofénica del perro, *ibid.* **32**: 270-272, 1945.

156. Nasio, J.: Acción del factor PP sobre la úlcera péptica experimental cincofénica, *Prensa méd. argent.* **32**: 720-722, 1945.

157. Merendino, K. A.; Judd, E. S.; Baronofsky, I.; Litow, S. S.; Lannin, B. G., and Wangenstein, O. H.: Influence of Caffeine on Ulcer Genesis: Experimental Production of Gastric Ulcer in Guinea Pigs and Cats with Caffeine, Together with a Study of Its Effect upon Gastric Secretions in Dog and Man, *Surgery* **17**: 650-666, 1945.

158. Roth, J. A., and Ivy, A. C.: The Pathogenesis of Caffeine-Induced Ulcers, *Surgery* **17**:644-649, 1945.

induced ulcers result from the proteolytic action of acid and pepsin on a gastric mucosa rendered more susceptible by "vascular" and "cellular" changes. The sequence of events is thought to be: vasodilatation and engorgement, vascular stasis, local anoxia, increased capillary permeability, transudation, extravasation of blood elements and decreased cellular nutrition.

Roth, Ivy and Atkinson¹⁵⁹ summarize their work on caffeine-induced "peptic" ulcer as follows: 1. Caffeine in relatively large doses causes acute and subacute ulceration of the gastric mucosa in cats. 2. Caffeine (80 to 250 mg.) stimulates gastric secretion in man and the cat but not in the dog. 3. Caffeine acts synergistically with histamine or alcohol in the stimulation of gastric secretion in man and the cat. 4. Caffeine-containing beverages stimulate gastric secretion in man. Coffee substitutes produced by roasting cereal contain secretagogues which stimulate gastric secretion in man. Coffee stimulates gastric secretion because of its caffeine content and because of other secretagogues (natural products of roasting or irritant volatile oils). 5. Caffeine and caffeine-containing beverages provoke a prolonged increase in the total output of acid in patients with peptic ulcer. 6. Five of a group of 50 normal, i. e., asymptomatic, human subjects responded to the caffeine test meal like patients with ulcer. Three of the 5 subsequently began to experience the ulcer type of distress, and 1 of these at the time of writing had an ulcer, as demonstrated by roentgenogram. 7. The evidence indicates that excessive use of caffeine-containing beverages may contribute to the genesis of "peptic" ulcer in the ulcer-susceptible person and will render the therapeutic management of the condition more difficult.

(d) Ulcer, Gastritis and Psychoneurosis: Among 45 consecutive patients with complaints referable to the upper part of the gastrointestinal tract 23 had roentgenologic evidence of duodenal ulcer. In these gastritis (diagnosed by gastroscopy) and psychoneurosis were not common. Of the other 22 patients, without roentgenologic evidence of ulcer, 80 per cent had some degree of psychoneurosis and 50 per cent had some degree of gastritis.¹⁶⁰

(e) Analysis of Gastric Content: In 200 patients with digestive disturbances encountered in an army hospital in the Pacific war zone

159. Roth, J. A.; Ivy, A. C., and Atkinson, A. J.: Caffeine and "Peptic" Ulcer: Relation of Caffeine and Caffeine-Containing Beverages to the Pathogenesis, Diagnosis and Management of "Peptic" Ulcer, *J. A. M. A.* **126**:814-820 (Nov. 25) 1944.

160. Montgomery, H.; Schindler, R.; Underdahl, L. O.; Butt, H. R., and Walters, W.: Peptic Ulcer, Gastritis and Psychoneurosis Among Naval Personnel Suffering from Dyspepsia, *J.A.M.A.* **125**: 890-894 (July 29) 1944.

by Rush, the odds in favor of a diagnosis of peptic ulcer increased as the free hydrochloric acid of specimens obtained from fasting stomachs rose above 50 to 75 units and as the volume of the content of the fasting stomachs rose above 120 cc.¹⁶¹

(f) Location: Of 960 benign gastric ulcers, only 20 (4.8 per cent) were located on the posterior wall.¹⁶²

Blum¹⁶³ adds a case of benign ulcer of the greater curvature to the 15 proved cases recorded in the literature.

(g) Medical Treatment: Alvarez¹⁶⁴ stresses the prophylactic importance of providing frequent feedings and antacid therapy during periods of emotional stress. Similarly, Reh fuss,¹⁶⁵ in a paper entitled "The Ulcer Life," emphasizes again the well known tendency of ulcer to recur and the importance of continuing treatment throughout the periods of quiescence. The patient must follow the rules as long as he lives. Emery¹⁶⁶ gives an equally broad and yet detailed outline of the philosophy, the theory and the practice of the treatment of the individual patient with peptic ulcer. Morlock¹⁶⁷ stresses the importance of acid in the formation of ulcer and points out the importance of patient cooperation. Collins¹⁶⁸ likewise emphasizes the role of nonabsorbable antacids, principally aluminum hydroxide gel, and the importance of supervised management, extending over the lifetime of the patient. A new compound, the basic aluminum salt of aminoacetic acid, has been found 42 per cent more efficient as an antacid than dried aluminum hydroxide gel U. S. P.¹⁶⁹ Rossett and Flexner,¹⁷⁰ using a simplified

161. Rush, A.: Fractional Gastric Analysis: A Simplified Technic with Interpretation of Results, *M. Clin. North America* **28**: 1516-1526, 1944.

162. Bonorino Udaondo, C.; d'Alotto, V., and Maciel, J. R.: *Ulceras de la cara posterior del estómago*, *An. Dispen. pub. nac. para enferm. d. ap. digest.* **7**: 335-349, 1944; *Prensa méd. argent.* **31**: 2213-2219, 1944.

163. Blum, S. D.: Peptic Ulcer of the Greater Curvature of the Stomach, *Am. J. Roentgenol.* **52**: 291-297, 1944.

164. Alvarez, W. C.: How to Avoid Flare-Ups of Peptic Ulcer, *J.A.M.A.* **125**: 903-904 (July 29) 1944.

165. Reh fuss, M. E.: The Ulcer Life, *Clinics* **3**: 480-493, 1944.

166. Emery, E. S., Jr.: The Treatment of the Patient with an Uncomplicated Peptic Ulcer, *M. Clin. North America* **28**: 1164-1172, 1944.

167. Morlock, C. G.: The Present Status of the Treatment of Uncomplicated Duodenal Ulcer, *Proc. Staff Meet., Mayo Clin.* **19**: 449-455, 1944.

168. Collins, E. N.: Use of Aluminum Hydroxide and Other Nonabsorbable Antacids in Treatment of Peptic Ulcer, *J.A.M.A.* **127**: 899-901 (April 7) 1945.

169. Krantz, J. C., Jr.; Kibler, D. V., and Bell, F. K.: The Neutralization of Gastric Acidity with Basic Aluminum Aminoacetate, *J. Pharmacol. & Exper. Therap.* **82**: 247-253, 1944.

170. Rossett, N. E., and Flexner, J.: The Effect of Certain Antacids in Man Measured by a Simplified Method for the Continuous Recording of Gastric p_H , *Ann. Int. Med.* **21**: 119-121, 1944.

method for the continuous recording of the p_H of the content of the human stomach, have again shown that milk and calcium carbonate, aluminum hydroxide gel U. S. P. and magnesia magma U. S. P. are long-acting antacids. Further emphasizing the "acid-pepsin" factor in peptic ulcer, Winkelstein¹⁷¹ successfully used the continuous intragastric drip of milk-sodium bicarbonate or aluminum hydroxide gel in treatment of 60 patients whose gastric ulcers were considered refractory to the Sippy program. A well illustrated paper on gastric ulcer as treated by duodenal feeding, gastroscopically controlled, is presented by Freeman.¹⁷²

Ivy¹⁷³ found that, whereas ulcer developed in 98 per cent of 114 Mann-Williamson control dogs in an average of thirty-eight months, 76 per cent of 25 such dogs treated daily for one year with enterogastrone did not show development of jejunal ulcer. Enterogastrone was given by injection to 43 patients. With 5 the injections were stopped because the patients complained of local pain. The immediate effects were not so rapid and did not produce as complete relief as those of strict ulcer management. The number of recurrences of ulcer distress in a group of 21 patients was reduced for a six month period from an anticipated 21 to 4. The author concludes that the preliminary results are sufficiently encouraging to warrant further study.

(h) Surgical Treatment: Heuer and associates¹⁷⁴ have published a book entitled "The Treatment of Peptic Ulcer Based upon Ten Years Experience at the New York Hospital." It cannot be reviewed here, but those interested will find that it illustrates clearly the trends of the past decade.

Eliason and Stevens¹⁷⁵ analyze the data on a consecutive series of 100 patients with peptic ulcer who were subjected to operation, with a mortality of 2 per cent. The indications for operation were perforation in 17 per cent, obstruction in 17 per cent, severe hemorrhage in 28 per cent and intractability, based on repeated recurrences of pain, in 55 per cent—which reads 69 per cent if one includes some of those with recurring hemorrhages. No attempt was made to evaluate the "permanent or five year cures."

171. Winkelstein, A.; Cornell, A., and Hollander, F.: The Medical Treatment of Peptic Ulcer Refractory to Sippy Therapy, *Surgery* **17**: 696-704, 1945.

172. Freeman, H.: A Gastroscopic Control of the Treatment of Gastric Ulcer by Duodenal Feeding, *Brit. J. Surg.* **32**: 303-308, 1944.

173. Ivy, A. C.: The Prevention of Recurrence of "Peptic" Ulcer: An Experimental Study, *Gastroenterology* **3**: 443-449, 1944.

174. Heuer, G. J.; Holman, C., and Cooper, W. A.: The Treatment of Peptic Ulcer Based upon Ten Years' Experience at the New York Hospital, Philadelphia, J. B. Lippincott Company, 1944, p. 118.

175. Eliason, E. L., and Stevens, L. W.: The Surgical Aspects of Peptic Ulcer, *S. Clin. North America* **24**: 1282-1289, 1944.

As Wangensteen¹⁷⁶ points out, ulcer is essentially the end effect of the digestive action of gastric juice on the gastric or the duodenal wall. It may occur in any one who has a stomach secreting an excessive amount of free hydrochloric acid. Ulcer occurs spontaneously in man but rarely does so in laboratory or domestic animals. Yet, by stimulation of the endogenous mechanism for the secretion of acid, ulcer may be produced almost at will in most of such animals. Under the influence of daily implantation of "histamine in beeswax" a torrent of acid secretion occurs which breaks down the ability of the cells to defend themselves. In consequence of the failure of neutralization of the acid, ulcer comes about. Erosion, which frequently occurs in the stomachs of normal persons, is undoubtedly a common precursor of ulcer. The probability is that the margin of difference between a person who has an ulcer and one who has not is small. Frequent feeding is the essence of a satisfactory conservative management. The long night fast constitutes essentially the most important defect in medical management. The surgical management of ulcer concerns itself primarily with medical failure and with the complications of ulcer. Subtotal gastric resection employing a short afferent duodenal loop is considered the procedure least likely to be complicated by stomal ulcer.¹⁷⁷ Brooks and Meacham,¹⁷⁸ in 57 patients with ulcer with intractable pain, pyloric obstruction and massive hemorrhage, carried out partial gastric resection, with 1 operative death. Of the group, 48 are living and well, 2 have residual symptoms and 1 shows no improvement. Five patients died one to three years postoperatively of conditions entirely irrelevant. The post-operative period of study has varied from one to ten years. Lewisohn¹⁷⁹ contrasts the incidence of jejunal ulcer following gastroenterostomy, 34 per cent, with the recurrence rate of 2.5 to 8 per cent for gastric resection and concludes that subtotal gastrectomy is the surgical treatment of choice for duodenal ulcer. The mortality rate did not exceed 1.5 to 3 per cent. Hinton,¹⁸⁰ on the basis of 85 cases in which he

176. Wangensteen, O. H.: Clinical Aspects of the Ulcer Problem with Special Reference to Definition of the Criteria of a Suitable Operation; the Importance of a Short Afferent Loop, and Results of Operation, *Minnesota Med.* **27**:714-722, 1944.

177. Wangensteen, O. H.: The Criteria of a Satisfactory Operation for Ulcer and Causes of Failure After Gastric Resection for Ulcer, *Minnesota Med.* **28**:66-70, 1945.

178. Brooks, B., and Meacham, W. F.: Partial Gastrectomy for Duodenal Ulcer, *South. M. J.* **38**:150-155, 1945.

179. Lewisohn, R.: Gastric Resection for Duodenal Ulcer, *Surg., Gynec. & Obst.* **80**:355-360, 1945.

180. Hinton, J. W.: Subtotal Gastrectomy in Medically Resistant Ulcers, *New York State J. Med.* **45**:291-295, 1945.

operated, covering a two year period, considers intractable pain not responding to intensive and adequate medical therapy to be the indication for surgical intervention, the frequency being about 10 per cent. Subtotal or partial resection with resection of the duodenal ulcer is the operation of choice. Lannin¹⁸¹ likewise concludes that the most satisfactory procedure is an extensive three-quarter gastric resection including the antrum and employing an efferent loop as short as possible. In 300 patients treated with this procedure, not a single recurrent jejunal ulcer was found. [The reviewers feel constrained to predict, however, that recurrences will develop in time.]

The percentage of patients with duodenal ulcers treated surgically at the Mayo Clinic declined from 38 in 1928 to approximately 13 in 1943, in which year 386 were so treated, with a mortality of 0.8 per cent. There were 157 treated by partial gastrectomy, with a mortality of 0.6 per cent. Of patients with gastric ulcers (145), 65 per cent had partial gastrectomy, with a mortality of 1.4 per cent.¹⁸² At the Massachusetts General Hospital from 1936 through 1943 primary elective subtotal gastrectomy was performed for peptic ulcer three hundred and twenty times, with 12 deaths, a mortality of 3.7 per cent. From 1936 through 1941 resection was performed for gastric ulcer fifty-five times, with no deaths, and resection for duodenal ulcer, one hundred and twenty-four times, with a mortality of 8.1 per cent. Leakage of the duodenal stump seems to have been the major factor in the high mortality. In 1942 and 1943, 51 patients underwent subtotal resection for gastric ulcer, with a mortality of 3.9 per cent. There were no deaths among 94 patients who underwent resection for duodenal ulcer.¹⁸³ In Rienhoff's¹⁸⁴ 260 consecutive cases of complicated duodenal ulcer in which the pylorus, the pyloric antrum and a portion of the acid-secreting mucosa of the fundus was resected, the immediate postoperative mortality was 2 per cent; complications developed in 32 per cent, and 66 per cent of the patients remained well. In a group of 79 patients who were treated by subtotal gastrectomy for duodenal ulcer prior to 1937 the mortality was 18.75 per cent. Since that time in 94 patients who were

181. Lannin, B. G.: Experimental Evaluation of a Satisfactory Operation for Ulcer, *Surgery* **17**:712-741, 1945.

182. Counseller, V. S.; Waugh, J. M., and Clagett, O. T.: Report of Surgery of the Stomach and Duodenum for 1943, *Proc. Staff Meet., Mayo Clin.* **19**:586-592, 1944.

183. McKittrick, L. S.; Moore, F. D., and Warren, R.: Complications and Mortality in Subtotal Gastrectomy for Duodenal Ulcer: Report on a Two-Stage Procedure, *Tr. Am. Surg. A.* **62**:531-561, 1944; *Ann. Surg.* **120**:531-561, 1944.

184. Rienhoff, W. F., Jr.: An Analysis of the Results of the Surgical Treatment of Two Hundred and Sixty Consecutive Cases of Chronic Peptic Ulcer of the Duodenum, *Ann. Surg.* **121**:583-599, 1945.

treated by gastrectomy the mortality has been 6.25 per cent, according to Colp¹⁸⁵ and his associates. Lahey's¹⁸⁶ impressions are that the incidence of stomal ulcer following gastroenterostomy is 15 per cent; the incidence following subtotal gastrectomy is about 2 to 3 per cent. Gastrojejunal ulcer should be treated medically first; if it is adherent to the transverse colon immediate operation is indicated, to avoid gastrojejunocolic fistula. Lahey does not advise that the Finsterer method of exclusion be followed because in 20 instances of such resection he observed the highest incidence of jejunal ulcer. The mortality from subtotal resection for ulcer should not be over 3 per cent. In 318 consecutive cases in which subtotal gastrectomy was done for ulcer 62 of the lesions were in the jejunum, 56 developed after gastroenterostomy and 6 after previous subtotal resection. The mortality from resection for gastric and duodenal ulcer was 2.8 per cent; that from resection for jejunal ulcer, 4.8 per cent.

A new and different surgical approach to the treatment of peptic ulcer has been suggested by Dragstedt,¹⁸⁷ i. e., supraphrenic bilateral vagotomy. In 10 cases of duodenal ulcer and 1 of gastric ulcer in which this procedure was tried the operation was well tolerated, although in 1 case postoperative nonfatal pneumonia occurred. The continuous night secretion in most of the patients before operation was abundant; in 7 it exceeded a liter in twelve hours. After the operation this secretion decreased 50 per cent in all patients. The number of patients subjected to this procedure has increased to approximately 100,¹⁸⁸ with 1 fatality (postoperative pneumonia) and with no known recurrence of ulcer to date.

In a subsequent report it is noted that 3 patients required gastroenterostomy because of persistence of symptoms of obstruction. These results suggest to the authors that gastroduodenal ulcer is a psychosomatic disease in which the central nervous system affects the stomach "via the vagi," probably chiefly through the greatly augmented secretion of gastric juice.¹⁸⁹ Apparently, little diminution of the nervous phase of gastric secretion is to be expected from partial vagotomy, and of course the chemical secretory phases are entirely unaffected.

185. Colp, R.; Klingenstein, P.; Mage, S., and Druckerman, L. J.: Subtotal Gastrectomy for Duodenal Ulcer, *Ann. Surg.* **120**:170-180, 1944.

186. Lahey, F. H.: Inflammatory Lesions of the Stomach and Duodenum, *J. A. M. A.* **127**:1030-1036 (April 21) 1945.

187. Dragstedt, L. R.; Palmer, W. L.; Schafer, P. W., and Hodges, P. C.: Supra-Diaphragmatic Section of the Vagus Nerves in the Treatment of Duodenal and Gastric Ulcers, *Gastroenterology* **3**:450-462, 1944.

188. Dragstedt, L. R.: Personal communication to the authors.

189. Dragstedt, L., and Schafer, P. W.: Removal of the Vagus Innervation of the Stomach in Gastroduodenal Ulcer, *Surgery* **17**:742-749, 1945.

The insulin test in the hands of Weinstein and his associates¹⁹⁰ proved to be an unfailing means of determining the persistence of part of the gastric vagus supply. In 6 clinical cases the condition was apparently not improved by partial vagotomy.

(i) Benign and Malignant Ulcer: Allen¹⁹¹ in a ten year experience found that 14 per cent of the lesions treated as benign gastric ulcer proved to be cancer. Wiley¹⁹² estimates that in 10 per cent of the cases the differentiation cannot be made.

(j) Massive Hemorrhage: Clark¹⁹³ discusses 112 patients with gross bleeding from the upper part of the digestive tract whom he encountered over a period of twenty years. In 94 of these the hemorrhage was attributed to ulcer, duodenal in 86 and gastric in 8. It is interesting that, of 1,254 patients with a history of ulcer whom he encountered in private practice, only 94 had had massive hemorrhage. Tidmarsh¹⁹⁴ recommends immediate and frequent feedings; barbiturates are preferable to opium. With continued and repeated bleeding, particularly when accompanied by arteriosclerosis, early surgical intervention should be considered.

Wakim and Mason¹⁹⁵ in an experimental study on trained dogs found that hemorrhage in amounts of approximately 25 per cent of the estimated total blood volume led to immediate cessation of intestinal activity and that recovery immediately followed replacement of the withdrawn blood or reinjection of the cells suspended in a quantity of Ringer's solution equivalent to the volume of the discarded plasma. The depletion of plasma proteins caused by repeated plasmapheresis also decreased intestinal activity, with a delay in the appearance of the feeding reaction.

Gregory, Ewing and Levine¹⁹⁶ observed that a drop in the systolic blood pressure to 70 or 80 mm. of mercury resulted in a rise of blood urea nitrogen to 25 mg. per hundred cubic centimeters. Blood given by

190. Weinstein, V. A.; Colp, R.; Hollander, F., and Jemerin, E. E.: Vagotomy in the Therapy of Peptic Ulcer, *Surg., Gynec. & Obst.* **79**:297-305, 1944.

191. Allen, A. W.: Gastric Ulcer and Cancer, *Surgery* **17**:750-754, 1945.

192. Wiley, H. M.: Gastric Ulcer, Benign or Malignant: A Review of Recent Literature, *Am. J. Surg.* **65**:104-111, 1944.

193. Clark, W. E.: The Significance and Management of Massive Bleeding from the Upper Gastro-Intestinal Tract, *South. M. J.* **38**:24-30, 1945.

194. Tidmarsh, C. J.: Medical Treatment of Ulcer Hemorrhage, *Canad. M. A. J.* **52**:21-24, 1945.

195. Wakim, K. G., and Mason, J. W.: The Influence of Hemorrhage and of Depletion of Plasma Proteins on Intestinal Activity, *Gastroenterology* **4**:92-101, 1945.

196. Gregory, R.; Ewing, P. L., and Levine, H.: Azotemia Associated with Gastrointestinal Hemorrhage, *Arch. Int. Med.* **75**:381-394 (June) 1945.

stomach tube raised the blood urea nitrogen level to 25 to 50 mg. per hundred cubic centimeters. The variations in the blood urea nitrogen due to ingestion of blood occurred more rapidly than the ones due to lowering of the blood pressure. Severe anemia did not cause azotemia. The combined effects of lowering the blood pressure and giving blood by stomach tube produced higher levels than would be expected from either alone. Azotemia may be due to decreased renal function caused by low blood pressure, dehydration and absorption of digested blood proteins; anemia is not a factor.

Levy¹⁹⁷ reports on 11 patients who were suffering severe hemorrhage and who were treated with the usual Sippy diet, to which was added a daily oral intake of from 100 to 200 Gm. of mixed amino acids. The serum protein returned to normal in an average of ten and two-tenths days. In a control group of 6 patients given the same diet without the amino acids the serum protein returned to normal in an average of nineteen days.

(*k*) Jejunal Ulcer: Morlock and Walters¹⁹⁸ describe three interesting jejunal ulcers attached to and burrowing deeply into the anterior abdominal wall. Sarason¹⁹⁹ reports the successful treatment of a recurrent gastrojejunal fistula.

(*l*) Perforation: Graham and Tovee²⁰⁰ report a mortality of 6.3 per cent in a series of 114 cases of perforated duodenal ulcer. Bacterial peritonitis is a late manifestation, since, of 59 cultures, 34 were sterile; in only 2 cases were colon bacilli obtained. Bisgard²⁰¹ found that subtotal gastric resection could be performed in the presence of diffuse soiling of the peritoneal cavity within twelve hours after the perforation of an ulcerating lesion of the stomach, the duodenum or the jejunum in patients in good condition, with a mortality lower than that observed in patients treated by simple closure with sutures.

Under the heading of noncancerous duodenocolonic fistula McClinton²⁰² describes a case thought to be the fifth in the literature since

197. Levy, J. S.: The Effect of Oral Administration of "Amino Acids" on the Hypoproteinemia Resulting from Bleeding Peptic Ulcer: Preliminary Report, *Gastroenterology* **4**:375-387, 1945.

198. Morlock, C. G., and Walters, W.: Peptic Ulcer Perforating into the Anterior Abdominal Wall, *Am. J. Surg.* **65**:133-137, 1944.

199. Sarason, E. L.: Recurrent Gastrojejunal Fistula, *J. Mt. Sinai Hosp.* **11**:282-285, 1945.

200. Graham, R. R., and Tovee, E. B.: The Treatment of Perforated Duodenal Ulcers, *Surgery* **17**:704-712, 1945.

201. Bisgard, J. D.: Gastric Resection for Certain Acute Perforated Lesions of Stomach and Duodenum with Diffuse Soiling of the Peritoneal Cavity, *Surgery* **17**:498-509, 1945.

202. McClinton, J. B.: Non-Malignant Duodeno-Colonic Fistula, *Canad. M. A. J.* **51**:434-436, 1944.

1885; in all the fistula followed rupture of a duodenal ulcer without operation. The report contains these interesting sentences:

The effect of stomach secretions on the colon was baffling. It appeared that hydrochloric acid trickling down was irritating to the colon.

On the writer's suggestion, Dr. D. W. Gordon Murray, of the Toronto General Hospital, conducted experiments on colostomy cases by injecting dilute hydrochloric acid. He states as follows:

"Since your suggestion regarding the effect of hydrochloric acid on the colon, I have had four colostomies in whom we tried injecting a dilute solution of HCl. It is my impression from this experience, that the HCl produces hyperperistalsis with secretion of mucus. In two, after going on for ten days or more, there was some blood in the mucus suggesting a rather active colitis as a result of the acid."

(m) Ulcer in Infancy and Childhood: Donovan and Santulli²⁰³ report 10 cases of peptic ulcer encountered at the Babies Hospital of New York in the period from 1930 to 1944 and suggest that the diagnosis probably would be made more frequently if it were realized that the condition occurs in this age group. Hemorrhage was present in 6 of the 10 children. Perforation and pyloric stenosis also were observed.

Florer and Ochsner²⁰⁴ observed a traumatic chylothorax complicated by fatal perforation of a duodenal ulcer in a 14 year old boy.

(n) Ulcer in Men in Military Service: Zetzel²⁰⁵ in an army station hospital found that, of 21,856 patients admitted in one year, 1,802 (8.1 per cent) were sent to the gastrointestinal section. Duodenal ulcer was found in 125 of these and gastric ulcer in 5, making an incidence of peptic ulcer of 7.2 per cent. Perforation and hemorrhage occurred in 6 of each group. Among 22,000 patients admitted over a two year period in a general hospital in Panama there were 66 (0.3 per cent) who had peptic ulcer, and 10 of these were suffering from acute perforations; there were no deaths. There was no seasonal incidence.²⁰⁶ Among 1,702 patients with abdominal symptoms Loder and Kornblum²⁰⁷ found only 82 with duodenal and none with gastric ulcers. The incidence was the same in white and colored patients. The percentages of peptic ulcer, acute and chronic gastritis and bacillary dysentery were

203. Donovan, E. J., and Santulli, T. V.: Gastric and Duodenal Ulcers in Infancy and in Childhood, *Am. J. Dis. Child.* **69**:176-179 (March) 1945.

204. Florer, R., and Ochsner, A.: Traumatic Chylothorax: Report of a Fatal Case Complicated by a Ruptured Duodenal Ulcer, *Surgery* **17**:622-629, 1945.

205. Zetzel, L.: Experiences with Peptic Ulcer in an Army Station Hospital, *Gastroenterology* **3**:472-479, 1944.

206. Harrell, W. B., and Wilson, R. O.: Ruptured Peptic Ulcer Among United States Troops in Panama, *Mil. Surgeon* **96**:336-342, 1945.

207. Loder, H. B., and Kornblum, S. A.: Duodenal Ulcer in a Large Army Camp: Incidence and Statistical Analysis, *Mil. Surgeon* **96**:492-497, 1945.

practically identical in colored and white patients admitted to a large army hospital.²⁰⁸

Feasby²⁰⁹ estimates that in the rapid clinical examinations of Canadian recruits for duodenal ulcer a 12 per cent error was made. In half of the 12 per cent ulcer was diagnosed but not confirmed; in the other half it was found when not expected. With regard to the usefulness of patients with ulcer, Feasby reports that "only 10 per cent of a selected group of men with healed ulcer were able to carry on indefinitely after return to duty, either in England or in Canada." Hook and Keane²¹⁰ in studying 306 Navy-enlisted men with duodenal ulcer found that 2 of 3 had had their symptoms prior to enlistment; there was no evidence to justify the belief that military service is conducive to the production of ulcer. Of the total group, 40.5 per cent were discharged, the others were sent to limited service and some were returned to regular duty.

Berk and Frediani²¹¹ interpret the prevalence of peptic ulcer in the Army as largely a reflection of its unsuspected frequency in the adult civilian population. The psychosomatic aspects, the influence of anxiety, tension and emotional unrest, seem to him unmistakable. Somewhat in accord with this view is an experiment in the rehabilitation of 100 soldiers with dyspepsia in which satisfactory results were obtained in 38 per cent of the 50 patients with peptic ulcer and in 70 per cent of the group as a whole. In the patients who did poorly, the factor of poor morale seemed to have been important. These studies confirmed those of Rook, who found that the higher the grade, the greater the percentage of men who could be salvaged—"only those who want to stay in the service will make a real attempt to regulate their life so that they can carry on."²¹² The incidence of peptic ulcer in 289 hospitalized dyspeptic patients was 34 per cent; the incidence in 682 outpatients was only 11 per cent. "Definite psychiatric factors were present in less than 25 per cent of the patients with ulcer and in less than 50 per cent of

208. Kirchner, A. A.: The Digestive Disturbances of the Negro Soldier as Seen in a Large Army General Hospital, *Rev. Gastroenterol.* **11**:397-408, 1944.

209. Feasby, W. R.: Peptic Ulcer in the Canadian Army (1940 to 1944), *War Med.* **6**:300-303 (Nov.) 1944.

210. Hook, F. R., and Keane, R. H.: The Plight of the Ulcer Patient in Military Service: Study of Three Hundred and Six Enlisted Personnel with Duodenal Ulcer, *U. S. Nav. M. Bull.* **44**:519-529, 1945.

211. Berk, J. E., and Frediani, A. W.: The Peptic Ulcer Problem in the Army, *Gastroenterology* **3**:435-442, 1944.

212. Rook, A. F.: Peptic Ulcer: Prognosis in Royal Air Force Patients, *Lancet* **1**:733-736, 1943; cited by Goldbloom, A. A., and Schildkrout, H.: Dyspepsia Regimen: A Method of Rehabilitation, *War Med.* **6**:24-26 (July) 1944.

those without ulcers." "Rehabilitation of the dyspeptic soldier presupposes a high standard of morale, a definite desire to serve the army and a lesion which can respond to appropriate medical and dietary management." [While the reviewers are in complete accord with the view that the personality of the patient is of great importance in the management of peptic ulcer, just as it is indeed in almost all chronic diseases or disorders, nevertheless it is premature to conclude that ulcer is a "psychosomatic disease."²¹³] Reference may be made to the excellent discussion of this subject by Kirk, which was briefly summarized last year.²¹⁴

A liberal convalescence diet was used, with no medicament except an occasional alkaline powder for symptomatic relief, in 478 patients with peptic ulcer admitted to the Hammond General Hospital. Clinical cures were obtained in 438. Thirty-seven patients not relieved were given a special diet containing bland foods, raw eggs, large amounts of butter, fresh greens and olive oil, which is considered to be rich in an antiulcer factor. Complete relief was obtained in 34 of the 37. [The results obtained seem to the reviewers to be those to be expected during hospitalization on almost any type of medical program and hence do not prove either the superiority of this regimen or the validity of the "vitamin A hypothesis."²¹⁵] Baumgartner²¹⁶ advocates the use of the original Sippy program.

213. Schildkrout, H.: Management of the Dyspeptic Soldier in a Staging Area, *War Med.* **6**:151-157 (Sept.) 1944.

214. Kirk, R. C.: Peptic Ulcer at Fort Sill, *Am. J. Digest. Dis.* **10**:411-413, 1943.

215. Gianelli, V. J., and Bellafore, V.: The Fundamental Importance of Diet in the Treatment of Peptic Ulcer in an Army General Hospital, *M. Clin. North America* **29**:706-713, 1945.

216. Baumgartner, M. M.: Peptic Ulcer in Naval Personnel, *U. S. Nav. M. Bull.* **44**:995-999, 1945.

(To Be Concluded)

Book Reviews

Structure and Function of the Human Body. By Ralph N. Baillif, Ph.D., and Donald L. Kimmel, Ph.D. Price, \$3. Pp. 328, with 286 illustrations. Philadelphia, London and Montreal: J. B. Lippincott Company, 1945.

This book presents anatomy and physiology in a concise and interesting form. The authors have retained all of the material necessary for the understanding of the basic course in anatomy and physiology. The great mass of details which often confuses the beginner has been eliminated. Such details could be added as supplemental material for lectures, if desired by the instructor.

The long introductory unit is so planned that it gives the student a comprehensive view of the entire anatomic field and the relationships involved. This unit is written with a minimum use of scientific terms and ends with an introduction to scientific terms. The glossary at the end of the book is one of its outstanding features.

Unit 2 is divided into discussions of the skeletal, muscular and circulatory systems. The drawings in this unit are particularly clear and form an excellent adjunct to the text.

Unit 3 deals with the digestive and respiratory systems, and unit 4, with the urogenital, endocrine and nervous systems. In both of these units the anatomy and physiology are so clearly presented and so closely correlated that the beginning student should have no difficulty in integrating structure and function. Drawings again help to enhance the explanations presented in the text.

The chapters are so planned that, although they have been grouped into units, the grouping is arbitrary and the method of presentation can be varied without loss of continuity in subject matter.

The only adverse criticism which might be presented, and this is a minor one, is that the book does not contain enough material to warrant its use as a text if only one course of anatomy and physiology is taught. It is a very good text for the initial presentation of the subject or for use as a review text.

Fitografia alergolica. By Jose Martorelli. Price unknown. Pp. 195. Buenos Aires, Argentina: Libería y editorial "El Ateneo," 1945.

This is a monograph dealing with the plants and pollens causing hay fever in the state of Cordova in Argentina. The introductory chapter gives a short botanical review of pollen and the process and functions of pollination. The third chapter deals with distribution of vegetation in Cordova. The fourth and fifth chapters describe the forms and structure of pollen, the methods of collecting pollen, the counting of pollen and several anemopollinometers, of complicated design. Chapter 6 constitutes half of the volume of the monograph and contains the most important feature of the book. It is a complete study of plants and pollens in Rio Cuarto and southeast Cordova. Included are many fine photographs of plants in their natural habitat and as dried specimens. There are also a large number of photographs of pollens. A pollination calendar gives valuable data. The most important hay fever season comprises the months of February and March, when the chenopods and amaranths pollinate. The grasses pollinate from November to May but do not produce large quantities of pollen.

This monograph is a valuable contribution to the knowledge of hay fever in South America. It should be of interest to allergists in the United States, physicians in Argentina and all those who will be called on to advise allergic globe trotters in their future travels.

Diagnostik und Therapie der Magen- Darmerkrankungen in Zwölf Vorlesungen (Diagnosis and Treatment of Gastrointestinal Diseases, in Twelve Lectures). By Fritz Hirschberg, M.D. Price, 30 Danish crowns. Pp. 352, with 110 illustrations. Copenhagen, Denmark: Einar Munksgaard, 1941.

This beautifully printed volume presents a series of informal yet polished lectures on the diagnosis and treatment of disorders of the stomach, small intestine, colon and rectum. The emphasis is on diagnosis, and there are many useful hints on the taking of histories, the physical examination and the interpretation of roentgenograms; in addition there is much that is instructive regarding the treatment of peptic ulcer, colitis and tumors, whether medical or surgical.

If the book has a defect, the defect is one which is shared with most medical literature of the present time and which ought to be outgrown in the near future, namely, a lack of appreciation of what medical statistics (in the best sense of the word) has to offer. An abundance of quantitative information is now becoming available from operations and necropsies and would often permit much more exact statements as to the relative frequencies of various complaints, the distribution of ulcers over the inner surface of the stomach, the probability that a given subjective complaint is accompanied with a particular organic change and so on. While much of this can be stated in percentages and does not presuppose more than sixth grade arithmetical achievements on the part of the reader, there lies beyond this the field of combinations, permutations and probability, familiar to students of first year algebra. With the help of these concepts it would often be possible to make much more definite statements regarding associations of symptoms and effects of treatment.

The author is to be commended for introducing on page 36 Forssell's nomenclature of the parts of the stomach. The wider use of this nomenclature would save anatomists the necessity of explaining, year after year, why the top of the stomach is called the bottom (*fundus*). This part is called the *forix* in Forssell's system, which is much better adapted to the roentgenographic appearance of the living stomach in the erect subject.

The two outstanding features of the book are its numerous roentgenographic illustrations and its readable, unaffected style. It should be inspiring and useful to any one interested in either the medical or the surgical aspects of gastrointestinal disease and deserves a translation into English.

Pulmonary Edema and Inflammation; an Analysis of Processes Involved in the Formation and Removal of Pulmonary Transudates and Exudates. Monographs in Medicine and Public Health, Number 7. By C. K. Drinker, M.D. Price, \$2.50. Pp. 106, with 27 illustrations. Cambridge, Mass.: Harvard University Press, 1945.

In this monograph Drinker has combined the studies that have been made by him and his associates at Harvard on the physiologic mechanisms and pathologic changes that are responsible for the functioning of the lung in the first place and in the second place for the production of disease. His own investigations he has correlated with the researches of others to produce a book which should be of inestimable value to the clinician. Edema of the lungs is a very common medical emergency with which the physician should be thoroughly acquainted, not only with how it is produced but also with how to combat it.

Lastly, Drinker discusses the problems of artificial respiration and reviews the various technics employed in maintaining artificial respiration. Cessation of respiration is an important, often dramatic and frequently catastrophic accident in medicine with which all physicians should be thoroughly familiar. The book is authoritative, practical and scientific.

Los Problemas del Cardíaco. By J. M. Hoyos, M.D. Price unknown. Pp. 153. México, D. F.: Revista de Medicina y Ciencias Afines, 1945.

Dr. Meneses Hoyos wrote this book with a single purpose: to disentangle the patient with cardiac disease from the web of prejudices and legends in which he lives, which perhaps contribute as much as the disease itself to the undermining of his spiritual strength and to the embitterment of his life. The book was written primarily for the general practitioner; yet its simple, clear, concise style will appeal as well to the specialist, the student and even the layman interested in medical literature.

Each chapter discusses a common and erroneous concept of heart disease without minimizing the germ of truth behind it. Nevertheless, fallacies are pointed out sharply in a simple and understandable manner through the judicious use of technical information.

The book begins with a discussion of the factors of inheritance in heart disease. This is followed by a section on prognosis of the cardiopathies, with emphasis on the fact that a useful, creative life need not be contraindicated in many of them. The efficiency of the circulatory mechanism at various altitudes is discussed, and the physiologic data are correlated with specific information regarding the effects of changes in atmospheric pressure on the diseased heart.

The dietary problem in cardiac disease is presented, with a simple explanation of the fundamental principles behind it. The chapters on tobacco and alcohol are sound discussions of their relation to the pathology of the heart. A section is dedicated to the work capacity of the diseased heart, in which Dr. Meneses Hoyos gives emphasis to the individual differences of each case and clarifies the fallacy of complete invalidism in all types of cardiac disease. The chapter on the problem of pregnancy in the woman with cardiac disease is followed by discussions of the risk of surgical intervention, of sudden death from cardiac disease and of arteriosclerosis and allied degenerative processes. In the final chapter the author presents his recommendations for the prevention of the cardiopathies as an individual and social problem.

To illustrate his discussions, Dr. Meneses Hoyos has drawn extensively on his own medical experience. The effectiveness of the presentation of the subject owes much to the clinical studies of cases which are summarized throughout the book.

Clinical Roentgenology of the Heart. By J. B. Schwedel, M.D. *Annals of Roentgenology*, Volume 18. Price, \$12.50. Pp. 400, with 732 illustrations. New York: Paul B. Hoeber, Inc., 1945.

There are many illustrations and diagrams in this new book, which present the problem of clinical roentgenography of the heart in the usual fashion. There is nothing particularly different in this presentation from that in other monographs or books already available. A correlation is made of the clinical, pathologic and roentgenographic data, but this is marred by either carelessness or the presentation of noncorrelating data. For example, on pages 64, 90 and 128 the electrocardiograms are improperly mounted (lead III of figure 36 C is upside down and reversed; essentially the same holds for those of figure 53 J and figure 72 C). Many illustrations are not very clear, e. g., figures 53 L, 119 D, 95 C, 93 A, 131 B, 73 A and 73 C. Fewer but better illustrations would make the book of greater value for the beginner than it can be now. The reader who is fairly well informed can recognize the errors and can profit somewhat from the book anyway.

The author unnecessarily brings in too many purely clinical statements based mainly on opinion. He states on page 129 that the diagnosis of failure of the right side of the heart is "confirmed by demonstration of enlargement of the right ventricular inflow tract" and, "The use of digitalis and diuretics provides only a poor or a temporary remission; the dyspnea and cyanosis are relieved by oxygen. Death usually follows bronchopneumonia or coma." These are among the remarks concerning chronic failure of the right side of the heart. Obviously, they are of

relatively little roentgenographic importance or are of questionable validity in many individual circumstances. The section on cardiology is relatively inadequate and adds little to the book. This is particularly true of the superficial remarks on therapy. It is difficult to recommend this book highly.

Preventive Medicine and Public Health. By Wilson G. Smillie, M.D.
Price, \$6. Pp. 607. New York: The Macmillan Company, 1946.

The reviewer knows of no one better qualified to write a book on preventive medicine and public health than Dr. Smillie. When one glances through the 600 odd closely printed pages, one realizes how large the subject has become. Naturally, there is some overlapping with what one finds in texts on bacteriology, infectious diseases and nutrition, but this can hardly be avoided. The sections on general matters, such as vital statistics and sanitation, are especially well done. On the whole the book is useful both for reference and for a survey of the whole subject.

News and Comment

WINNER OF 1946 CASH PRIZE AWARD OF NATIONAL GASTROENTEROLOGICAL ASSOCIATION

The winning contestant of the \$100 prize offered by the National Gastroenterological Association for the best unpublished manuscript on gastroenterology or an allied subject is Capt. Irving B. Brick, Medical Corps, Army of the United States, for his paper, "Radiation Effects on the Human Stomach: A Preliminary Report." The check was presented to Captain Brick at the annual banquet of the association, held at the Hotel Pennsylvania on Thursday evening, June 20, 1946.

Certificates of merit were awarded to Dr. Frank L. Apperly, Richmond, Va.; Dr. William Nimeh, México, D. F., Mexico, and Dr. Juan Nasio, Rosario, Argentina.

The winning paper, as well as the papers by physicians who received certificates of merit, will be published in the *Review of Gastroenterology*.

ANNUAL SESSION OF AMERICAN COLLEGE OF PHYSICIANS

The twenty-eighth annual session of the American College of Physicians will be held in Chicago, April 28 through May 2, 1947. The officers are: Dr. David P. Barr, New York, president; Dr. LeRoy H. Sloan, Chicago, general chairman, and Mr. Edward R. Loveland, executive secretary, 4200 Pine Street, Philadelphia 4.

TROPICAL ULCERS AND CUTANEOUS DIPHTHERIA

LIEUTENANT COLONEL AVERILL A. LIEBOW

MAJOR PAUL D. MACLEAN

LIEUTENANT COLONEL JOHN H. BUMSTEAD

AND

MAJOR LOUIS G. WELT

MEDICAL CORPS, ARMY OF THE UNITED STATES

INTRODUCTORY AND HISTORICAL NOTES

ULCERATIVE lesions of the skin occur frequently in the tropics. There is one type of ulcer, among soldiers who took part in the Pacific island campaigns, from which virulent *Corynebacterium diphtheriae* was often isolated. This paper is particularly concerned with lesions of this type. Typically, they are deep and have a punched-out appearance. They have been called "ecthyma" by some. This type of lesion is identical with the so-called desert sore of Northern Africa and Asia, of which the diphtheritic origin has been recognized and which frequently occurred in Allied and German soldiers. Evidence will be presented concerning the infected skin as a source of nasopharyngeal as well as cutaneous diphtheria, not only among military but also in large civilian populations to which the military have returned. Aside from these epidemiologic considerations these ulcers are of particular interest since neuritis and myocarditis are among the sequelae. There will also be presented data indicating the existence of a tremendous reservoir of diphtheria among natives in the tropics, which is largely cutaneous, which affects chiefly young children and which accounts in large measure for the remarkably accelerated acquisition of a state, in these natives, in which they do not react to the Schick test.

Other varieties of ulcerative lesions also are extremely common among natives in tropical countries. Cutaneous leishmaniasis, which may become ulcerative, is widely distributed in tropical countries but has not been described in the Solomon Islands,¹ and we have been unable to detect *Leishmania* bodies in any of the material derived from this region. Among natives of the South Pacific archipelagos,

From the Thirtieth General Hospital.

1. Strong, R. P.: *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*, ed. 6, Philadelphia, The Blakiston Company, 1942.

Clifford James² has observed a common type of "tropical phagaedenic ulcer." It tends to reach a very large size and to have a deeply undermined edge and a foul necrotic base containing fusiform bacilli and spirochetes during the acute phase. The occurrence of "cocci" and "diphtheroids" is mentioned, but there were no detailed studies of the latter. James, in his description of 892 cases, noted that if the diet was low in vitamins, as it was in New Britain, the ulcers were numerous and severe and involved an earlier age group. This type of lesion has not been observed among American troops. Frequent among the latter, however, is a superficial saucer-shaped impetiginous lesion in which beta hemolytic streptococci and staphylococci are usually found. With these types of ulcers this paper will not primarily be concerned.

Diphtheria of the Skin in Temperate Climates.—In ordinary clinical practice diphtheria of the skin occurs as a complication in approximately 1 per cent of cases of nasopharyngeal diphtheria.³ This was true in a study of 3,000 cases by Rolleston in England and in a review of approximately 2,000 by Adler at St. Anne's in Vienna, Austria. The condition was much more frequent and severe in the early part of the nineteenth century, when leeches were used in the treatment of diseases of the throat. In Rolleston's³ series the philtrum was most commonly involved, followed by the pinna, the fingers and the external malleoli. The lesions were polymorphic but characteristically tended to become deep chronic ulcers that were resistant to treatment.

Diphtheria of the Skin in the Tropics.—In the Middle East and in Northern India diphtheritic lesions of the skin appear to have occurred frequently and out of all proportion to the amount of clinically manifest nasopharyngeal diphtheria (table 1). This has been true not only of the natives but also of the military population stationed in these districts. During the Egyptian and Palestine campaigns of World War I, Craig⁴ reported finding "toxigenic" corynebacteria in 67.5 per cent of the "desert," "septic" or "Veldt" sores. The occurrence of paralysis was observed by Walshe⁵ in troops evacuated from the same territory. During 1940 the condition was again prevalent

2. James, C. S.: Tropical Phagaedenic Ulcer in the Pacific, Tr. Roy. Soc. Trop. Med. & Hyg. **31**:647-666, 1938.

3. Rolleston, J. D.: Acute Infectious Diseases, London, William Heinemann, 1925.

4. Craig, C. M.: A Study of the Etiology of the "Desert," Septic or Veldt Sore Amongst European Troops and Its Association with Faucial Diphtheria, Lancet **2**:478-479, 1919.

5. Walshe, F. M. R.: Post-Diphtheritic Paralysis: Note on a Form Following Cutaneous Diphtheria, Lancet **2**:232-233, 1918.

TABLE 1.—Cutaneous and Nasopharyngeal Diphtheria Originating in the Tropics

I	II	III	IV	V	VI	VII	
References *	Apparent Source	Total Number of Ulcers Studied	Number of Diphtheric	Proportion of Strains from III Virulent	Other Types of Diphtheria	Proportion of Strains from V Virulent	Comment
Craig ¹	Egypt and Palestine, 1917-1918	197	129	See VII	Throat (approx.)..... 452 Carriers..... 33 "Contacts"..... 49	See VII	Organisms in III and V stated to be "toxigenic"
Cameron and Muir ⁶	Northern Palestine, 1940	...	66	8/11	Throat..... 79 Nose..... 26 Carriers..... 78	One patient in IV reported avirulent; later neuritis developed
MacGibbon ⁷	Middle East, 1943	...	3	...	Facial..... 62 Otitis..... 4 Fracture..... 1 Burn..... 1	High proportion of neurologic complications (see table 9)
Fleck, Kellam and Kilppen ⁹	Middle East, 1943	Cultures of "other Veldt sores" not reported	4	See VI	Facial..... 48 Carriers..... 80 "Myocarditis"..... 1 "Paralysis"..... 6	33/38 8/10	"Myocarditis" and "paralysis," presumably postdiphtheric but without demonstration of bacteria
Bensted ¹⁵	Northwest India, 1935	...	31	31	Facial..... 15 Carriers..... 19	15/15 15/19	
Hamburger ¹³	Northeast India, 1938	88	3	2/3			
Present report ¹	Islands of the Pacific, 1943-1944	790	174	145/173	Throat..... 64 Nose..... 5 Nose and throat..... 1 Carriers..... 24	60/62 5/5 1/1 12/23	See details in table 13 and figure 15

* All of these reports except that of Hamburger concern military populations. In Burma many soldiers with diphtheric ulcers have been carefully studied by C. S. Livingood and his co-workers (personal communication).

† In column V are included all cases in which organisms were found in the nasopharynx.

among British troops stationed in Palestine and was thoroughly investigated by Cameron and Muir.⁶ A more recent report concerning diphtheria in the British army of the Middle East was presented by MacGibbon,⁷ who likewise noted the disproportionately large numbers of cutaneous lesions and remarked about how often the disease is missed. It was also observed among returned soldiers by Williams.⁸ Four cases of diphtheritic "Veldt" sore were found, together with 48 cases of pharyngeal diphtheria, by Fleck, Kellam and Klippen⁹ among German prisoners of war captured in Africa and confined to a prison camp at Aliceville, Ala. In Algeria,¹⁰ from August to September 1943, there was an epidemic of 4,000 cases of tropical ulcer, the cause of which was stated to be unknown. Whether adequate cultures were made to detect *C. diphtheriae* was not stated.

Northern India appears to be another great endemic center of cutaneous diphtheria. Epidemics of tropical ulcers are said to have "swept like a plague" through Assam.¹¹ Diphtheritic sores have been described among natives of the Chittagong hills,¹² and Hamburger¹³ found 3 per cent of the ulcers in a neighboring district to contain *C. diphtheriae*. Grindlay¹⁴ observed them in troops fighting in the adjacent Burmese jungle but considered them to be associated with spirochetal infections and vitamin deficiency, although no detailed etiologic investigations were reported. On the other side of Northern India, in the "Northwest Frontier Province," diphtheritic ulcers and the associated conditions that were prevalent among soldiers in British regiments were carefully studied by Bensted.¹⁵

6. Cameron, J. D. S., and Muir, E. G.: Cutaneous Diphtheria in Northern Palestine, *Lancet* **2**:720-723, 1942.

7. MacGibbon, T. A.: Diphtheria in the Middle East: Some Observations on Seventy-One Cases, *Edinburgh M. J.* **50**:617-625, 1943.

8. Williams, H. C. M.: Cutaneous and Conjunctival Diphtheria, *Brit. M. J.* **2**:416-417, 1943.

9. Fleck, S.; Kellam, J. W., and M. Klippen, A. J.: Diphtheria Among German Prisoners of War, *Bull. U. S. Army M. Dept.*, 1944, no. 74, pp. 80-89.

10. Epidemic of Tropical Ulcer in Algeria, *Bull. U. S. Army M. Dept.*, 1944, no. 75, pp. 13-14.

11. Diphtheria, *Bull. U. S. Army M. Dept.*, 1944, no. 76, p. 21.

12. Pasricha, C. L., and Panja, G.: Diphtheritic Ulcers of the Skin: The "Garigha" of Chittagong Hill Tracts, *Indian J. M. Research* **27**:643-650, 1940.

13. Hamburger, H. J.: Observation on the Pathology and Therapy of the So-Called Frontier Sore, *Indian M. Gaz.* **74**:151-155, 1939.

14. Grindlay, J. H.: Treatment of Skin Infections in the Assam-Burma Jungle, *Bull. U. S. Army M. Dept.*, 1944, no. 74, pp. 74-80.

15. Bensted, H. J.: A Limited Outbreak of Diphtheria Exhibiting Both Cutaneous and Faucial Lesions, *J. Roy. Army M. Corps* **67**:295-307, 1936.

The lesions described by these writers bear remarkable resemblance to the deep, "punched-out" type of tropical ulcers seen by us in troops evacuated from the Solomon Islands, Saipan (one of the Marianas) and Leyte (one of the Philippine Islands).

MATERIALS AND METHODS

General Phases.—The earlier investigations of the ulcers were made at the Thirty-Ninth General Hospital from March 1943 to July 1944, during which time the ulcers of 85 patients were recognized as diphtheritic and studied. Most of the patients were derived from the Twenty-Fifth and Forty-Third Divisions. The second phase was carried out from Sept. 15 to Oct. 31, 1944 in the New Hebrides with the Twenty-Seventh Division shortly after the evacuation of the division from the Saipan campaign. During this interval the diphtheritic tropical ulcers of 89 patients were studied. A survey was made of the incidence of the ulcers, of the diphtheria carrier rates and of other pertinent data in these divisions during rest periods. At the same time preliminary investigations were carried out on Tonkinese and Melanesian natives of these islands in pursuit of early studies on the results of the Schick test among adult Solomon Islanders. Later, in the Marianas, these were amplified among the Chamorros. Then also came the opportunity for confirmatory observations on soldiers evacuated from Leyte.

Types of Investigation.—During the earlier part of the study, from March to September 1943, intensive parasitologic and bacteriologic studies were made, including anaerobic cultures, dark field examinations, potassium hydroxide smears and cultures for fungi and Giemsa stains for protozoa. Leishmania bodies in particular were searched for both in the Thirty-Ninth General Hospital and in the Saipan groups. Neither protozoa nor spirochetes were found, and fungi, such as *Monilia* and *Epidermophyton*, were only rarely encountered. When the frequent presence of *C. diphtheriae* became apparent, a special procedure was employed to obtain evidence concerning the epidemiologic aspects of lesions associated with this organism and the pathogenesis of these lesions, and the bacteriologic methods were simplified to concentrate on the detection of the organism.

A standard form of clinical record was used in each instance, which included questions concerning the patient's home and military history, with special emphasis on any exposure to diphtheria (sore throats and ulcers occurring in the organization), previous Schick test, record of immunization, or sore throat occurring in the patient himself, and questions designed to elicit evidence of neurologic damage and also the mode of origin and the course of the ulcer to the time of the patient's admission to the hospital. In each instance the size of the lesion at the time of admission was recorded, and follow-up data under various modes of treatment were collected. Cultures of material taken from the ulcers were made at intervals, and cultures of material taken from the nose and the throat were made routinely. The Schick test was made in all instances except those in which concurrent nasopharyngeal diphtheria demanded the immediate administration of antitoxin. Before the patient was discharged from the hospital, a physical examination, with emphasis on the neurologic aspects, was again performed. It is the review of these systematic records that is the basis of the tables presented in the text.

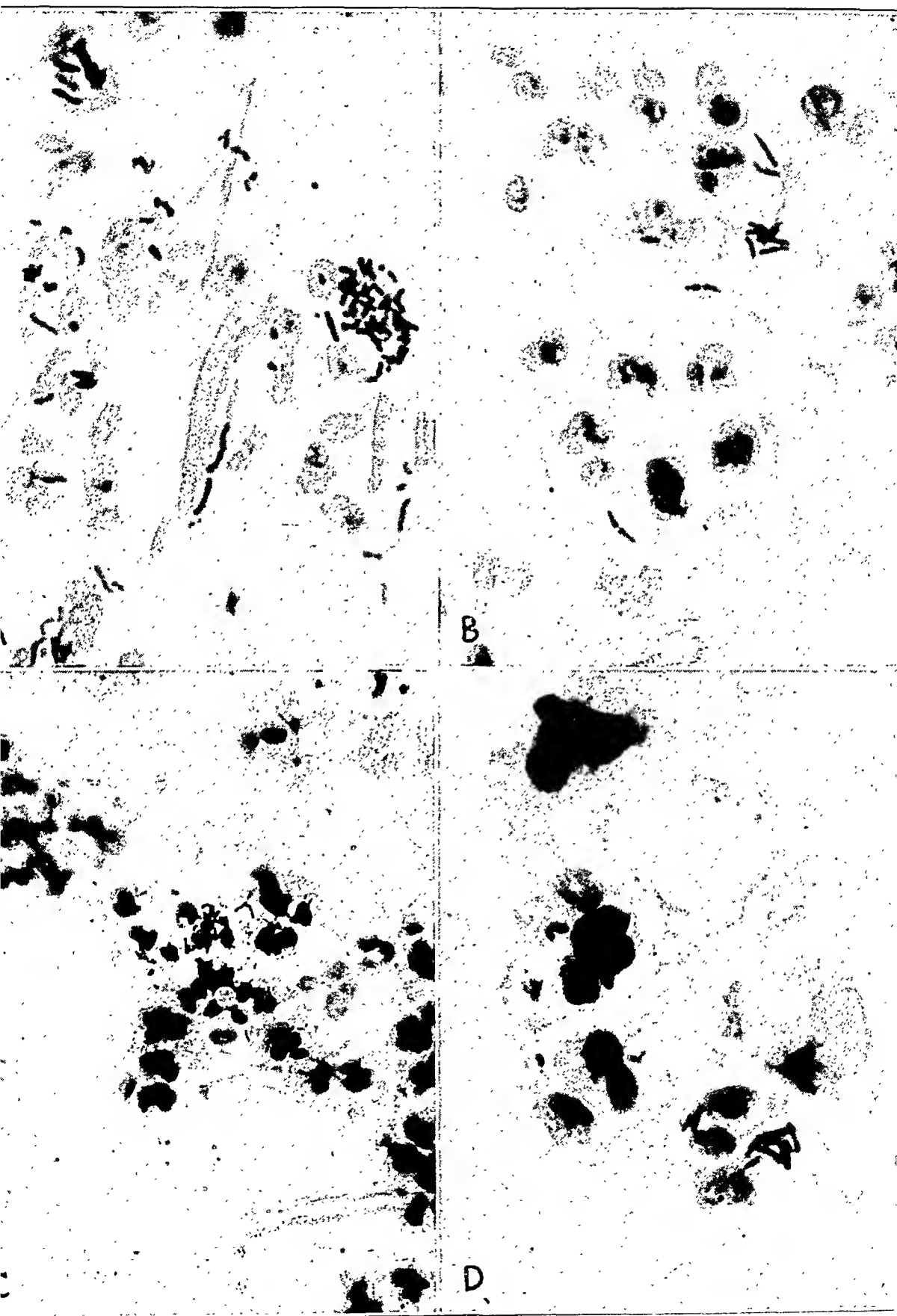


Figure 1

(See legend on opposite page)

Methods of Culture and Identification of C. Diphtheriae.—The simplest methods of culture are effective. If the ulcer is relatively clean and not crusted, material for culture may be taken from the base directly, without further preparation; it is unnecessary to apply alcohol or other agents. In hospital cases, as a routine procedure, it is more satisfactory to apply a warm pack of isotonic solution of sodium chloride to the lesion for from three to twenty-four hours, which helps to remove any excess of exudate, fibrinous crust, or residue of ointments that may previously have been applied. Exudate is then removed from the base of the ulcer for smear and culture. Löffler's serum slants or blood agar may be used as mediums. Tryptose agar without dextrose,¹⁶ containing 5 per cent human blood, was employed.

In direct smears from the lesions the organisms identified as *C. diphtheriae*, as a rule, are differentiable from diphtheroids, since they are longer, more pleomorphic, with slender and club-shaped forms, more granular and less intensely gram-positive. They are often found within the polymorphonuclear leukocytes of the exudate (fig. 1). Sometimes they are extremely numerous and are the predominant element of the bacterial population, but usually there is an admixture of gram-positive cocci in chains and clumps. In exudates the organisms frequently are stouter than in the classic descriptions, which are based on the appearance of the bacteria on Löffler's medium after twelve to twenty-four hours of cultivation. The bacteria from the cutaneous lesions assume the classic forms when grown on this material.

With the Saipan group an attempt was made to determine how well purely morphologic criteria when applied by an experienced observer would bear the test of subsequent bacteriologic investigation. In smears of exudate from 150 ulcers the presence or the absence of *C. diphtheriae* was correctly diagnosed one hundred and twenty-five times (83.3 per cent). In 10 instances (6.6 per cent) Klebs-Löffler bacilli were not seen on direct smears but were found on cultures. In 15 instances (10 per cent) gram-positive pleomorphic bacilli were incorrectly diagnosed as *C. diphtheriae* from the smear. This demonstrates that with experience a reasonably accurate guess can be made which may have application under field conditions when facilities for culture are not available.

In smears made from the Löffler serum slant after eight to twelve hours of incubation *C. diphtheriae* appears in long slender pleomorphic forms which make

16. Manual of Dehydrated Culture Media and Reagents, Detroit, Difco Laboratories, Reprint, 1941, p. 91.

EXPLANATION OF FIGURE 1

A (patient Y56), exudate from diphtheritic ulcer. Many of the pleomorphic toxigenic bacilli are intracellular. $\times 1,100$.

B (patient Y56), exudate from another ulcer. Note "double suppository" forms of *C. diphtheriae* sometimes observed in direct smears of exudates. $\times 1,100$.

C (patient Y57), exudate from diphtheritic ulcer. *C. diphtheriae* is seen within the leukocytes. See figure 14, *A*. $\times 500$.

D (patient Y57), exudate from diphtheritic ulcer. Note intracellular position of pleomorphic gram-positive bacilli. $\times 1,100$.

In this and subsequent legends Y in the designation of the patient means that the lesion developed in the Solomon Islands, and S, that it developed in Saipan.

it possible to differentiate them tentatively from the generally much shorter and thicker diphtheroids, pending the results of the other tests. In our experience a positive preliminary reading of the slant was sufficiently reliable to warrant isolating the patient.

Although the technic¹⁷ of isolating *C. diphtheriae* is exceedingly simple, certain precautions should be employed. The use of blood agar plates is advantageous, since the isolated colonies can be studied and picked for subculture within twenty-four hours. The essentials of the technic are:

1. The p_H of the agar must be adjusted to 7.6 before sterilization. *C. diphtheriae* grows much better on slightly alkaline mediums.
2. The medium must be cooled to 45 C. or less before the blood is added. If the blood is overheated, the narrow ring of hemolysis characteristic of *C. diphtheriae mitis* may be obscured, and the colonies are then less easily distinguished from those of staphylococci and diphtheroids.
3. Good streaking technic must be employed.

This method is sensitive and accurate only if well isolated colonies are obtained. The best method for learning to identify these organisms is to study known strains at various intervals in comparison with staphylococci and diphtheroids, which offer the greatest difficulty in gross recognition of the colonies. On the blood agar plate *C. diphtheriae* is easily distinguished from certain hemolytic corynebacteria that are commonly observed among troops and natives in the tropics. These probably belong to the *Corynebacterium ovis* and *Corynebacterium pyogenes* group and are the subject of a separate report. The designation "*Corynebacterium hemolyticum*" has tentatively been applied to this organism. On Löffler's medium the organism closely resembles *C. diphtheriae*, but on blood agar plates during the first twenty-four hours the colonies of *C. hemolyticum* come to be surrounded by a large zone of beta hemolysis which renders them easy to identify.

All the strains of *C. diphtheriae mitis* that were tested, a total of 91 from patients with cutaneous diphtheria and 49 from patients with nasopharyngeal diphtheria and carriers, fermented dextrose. Maltose was usually fermented within twenty-four hours, but with some of the strains there was complete or partial reversion of the medium to alkalinity by the end of the week. Most of these strains fermented galactose at least partially, and the reversion phenomenon was observed in a few. Sucrose broth in rare instances showed a transient slight reduction in p_H of the medium (not below 7.0) but became strongly alkaline by the fourth to the seventh day. Transient acidity (not below p_H 6.8) also developed in lactose broth. These fermentation reactions occurred whether or not the strain was toxigenic.

All strains were tested for toxigenicity by the controlled intracutaneous method of Fraser and Weld,¹⁸ using the guinea pig and in some instances the rabbit being used. The results obtained by this method were unequivocal. All organisms found to be atoxic were tested again. The results of the second examination invariably agreed with the first.

17. Hewlett, R. J.: *Corynebacterium Diphtheriae and Diphtheroid Organisms*, in Bulloch, W., and others: *A System of Bacteriology in Relation to Medicine*. Medical Research Council, London, His Majesty's Stationery Office, 1930, vol. 5. pp. 67-150.

18. American Public Health Association: *Diagnostic Procedures and Reagents*, New York, American Public Health Association, 1941.

Correlation of Morphologic and Cultural Characteristics with Toxicogenicity.—Considering strains from the tropical ulcers, 84.1 per cent of the strains of hemolytic corynebacteria with these morphologic and colonial characteristics and fermentative powers proved toxigenic. By generally accepted definition the remaining 15.9 per cent must be considered as *C. diphtheriae*, nontoxigenic. The atoxic strains were relatively more common in carriers (table 13). We did not encounter any of the nonhemolytic gravis¹⁹ strains. All the many strains of nonhemolytic corynebacteria that were studied by us (44 strains) proved to be nontoxigenic. Two of these had the fermentative but not the morphologic properties of *C. diphtheriae*.

TABLE 2.—*Bacterial Flora of "Tropical Ulcers" and of Certain Other Dermatitides (790 Patients)**

Organism	27th Division (288 Patients)	25th and 43d Divisions †	
		Group A (278 Patients)	Group B (224 Patients)
<i>Corynebacterium diphtheriae</i> , toxigenic.....	75	65	5
<i>Corynebacterium diphtheriae</i> , nontoxigenic.....	13	6	9
"Diphtheroids"	18	69	49
Hemolytic corynebacteria of <i>Corynebacterium py-</i> <i>ogenes</i> group	9	21	19
Beta hemolytic streptococcus.....	145	126	133
<i>Staphylococcus albus</i>	28	138	100
<i>Staphylococcus aureus</i>	183	99	132
<i>Alcaligenes faecalis</i>	22	18	35
<i>Escherichia coli</i>	0	11	2
<i>Alpha streptococcus</i>	9	6	3
<i>Gamma streptococcus</i>	0	6	0
<i>Pseudomonas pyocyanea</i>	4	5	7
<i>Proteus vulgaris</i>	1	3	2
<i>Neisseria catarrhalis</i>	0	0	1
Unidentified gram-negative bacillus.....	0	0	2
Percentage containing <i>Corynebacterium diphtheriae</i>	30.6	25.5	6.2
Percentage containing toxigenic <i>Corynebacterium</i> <i>diphtheriae</i>	26.0	23.4	2.2

This table refers to all ulcerative dermatitides of the skin. Information concerning the proportion of these having the morphologic aspects of the typical "tropical ulcer" or ecthyma, which is the main subject of this report, is available only for the Twenty-Seventh Division and is presented in the text.

* Results of first examination of each patient are recorded.

† For definition of groups see text.

BACTERIOLOGIC AND MORPHOLOGIC ASPECTS OF TROPICAL ULCERS

Bacteriologic Observations.—A list of the bacteria present in all ulcerative and moist desquamative cutaneous lesions of which the bacterial flora was ascertained is presented in table 2. Many of these were of the shallow or impetiginous type and were not classed as typical of the diphtheritic ulcer as described in the next section. The relationship between the morphologic and the bacteriologic aspect is

19. Anderson, J. S.; Happold, F. C.; McLeod, J. W., and Thomson, J. G.: On the Existence of Two Forms of Diphtheria Bacillus—*B. Diphtheriae Gravis* and *B. Diphtheriae Mitis*—and a New Medium for Their Differentiation and for the Bacteriological Diagnosis of Diphtheria, *J. Path. & Bact.* **34**:667-681, 1931.

considered in a later section. In table 3 is recorded the bacterial flora of those lesions in which *C. diphtheriae* was actually found.

It is interesting to note that the shorter the interval between the time that the lesion is acquired and the time that it is cultured the higher the incidence of *C. diphtheriae* and the greater the ratio of toxigenic to atoxic bacilli. This relationship is brought out in table 2. In it the Thirty-Ninth General Hospital series has been subdivided into two groups. Group A represents the patients studied before Feb. 15, 1944 and comprises largely members of the Twenty-Fifth

TABLE 3.—*Bacterial Flora of Diphtheritic Ulcers of the Skin (Primary Isolations)*

	Coryne- bacterium Diph- theriae (Pure Culture)	Coryne- bacterium Diph- theriae (4 Plus or 3 Plus)	Associated Bacteria				
			Diph- theroids	Beta Hemo- lytic Strepto- coccus	Coryne- bacterium Hemo- lyticum	Staph- ylococcus Albus	Staph- ylococcus Aureus
<i>C. diphtheriae</i> , toxigenic (total, 145).....	6	84	6	63	14	45	49
<i>C. diphtheriae</i> , nontoxigenic (total, 28).....	..	16	1	13	5	9	13

Numbers refer to patients.

The data have been subdivided according to toxigenic and nontoxigenic strains.

"4 Plus or 3 Plus" refers to predominance of the bacteria.

TABLE 4.—*Type of Lesion from Which C. Diphtheriae Was Cultivated*

Lesion	C. Diphtheriae	
	Virulent	Avirulent
Deep ulcers.....	114	17
Shallow ulcers or impetiginous lesions.....	17	8
Deep tract.....	4	..
Diffuse desquamative and ulcerative dermatitis.....	4	..
Paronychia *.....	2	..
Total †.....	141	25

* In another patient paronychia complicated a diffuse desquamative and ulcerative dermatitis (patient Y 5, fig. 74).

† No exact data concerning the morphologic character of the lesions are available in 8 of the earlier cases.

Division. This group came to the rest area during November 1943, approximately six weeks after cessation of combat (when most of the ulcers were acquired). Group B consists largely of members of the Forty-Third Division evacuated to the rest area after Feb. 15, 1944, some twenty weeks after their combat experience. The Twenty-Seventh Division group is comparable to group A, in that the studies were carried out some four to six weeks after the Saipan campaign.

The decrease in the proportion of toxigenic to atoxic strains of *C. diphtheriae* with time is of interest. In the Thirty-Ninth General Hospital group, 40 of 43 (93 per cent) diphtheritic ulcers of less

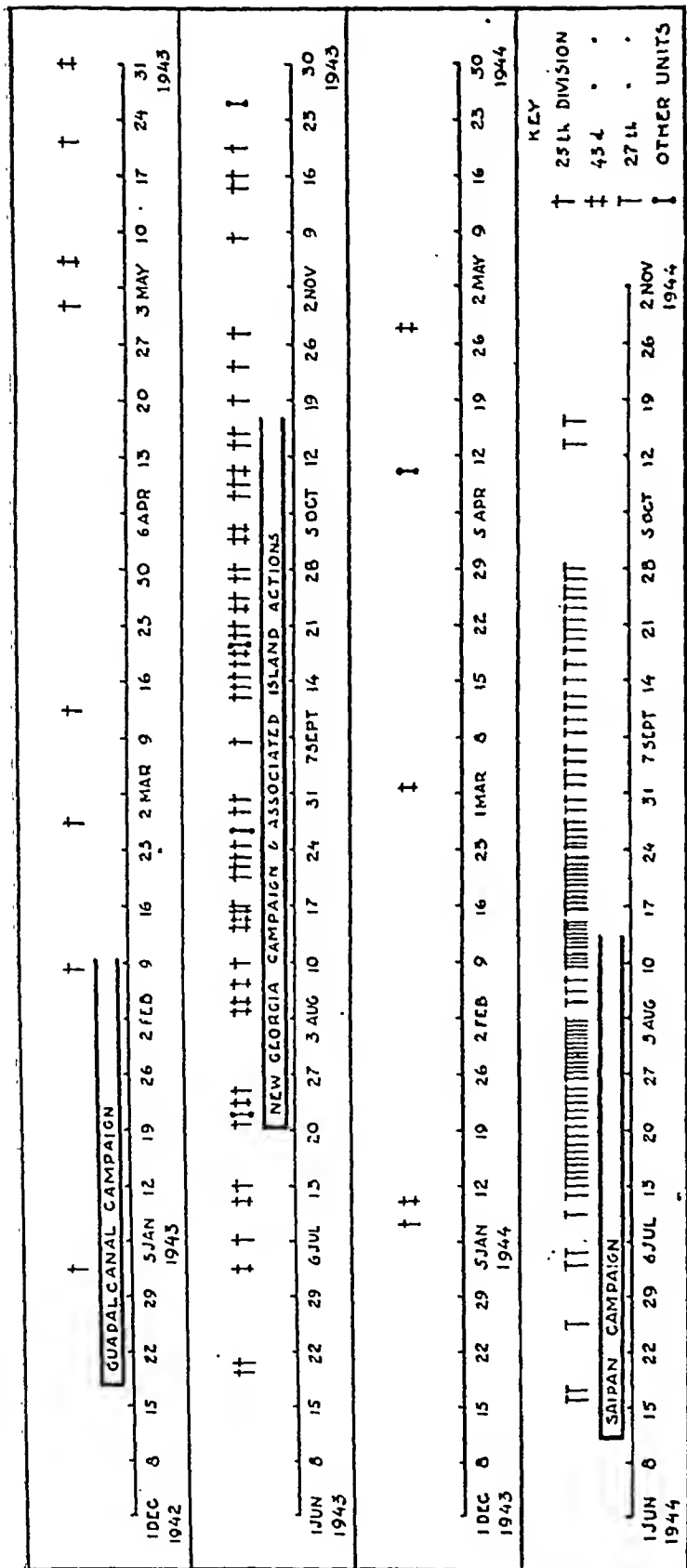


Fig. 2.—Diphtheritic tropical ulcers. Onset in relation to the campaigns. The dates of onset of the ulcers as estimated by the patients are represented. There are certain inaccuracies; e. g., the clinical records of 2 patients indicated that the disease began on a certain island before that island was actually taken by the troops. These are nevertheless represented on the chart on the date indicated by the patients' statement. It is obvious, therefore, that some of the dates of onset should be shifted to the right. The data are incomplete in the following respects:

1. All patients evacuated during and after the Guadalcanal campaign until approximately March 13, 1943 (and some after this date) went to other installations. The first section of the chart is therefore included only for the purpose of reference.
 2. The records of some of the earlier patients are incomplete.
 3. Systematic cultures of all ulcerative lesions of the skin were not made in this hospital until June 1943.
 4. Many patients evacuated during action in New Georgia likewise never reached this installation.
 5. With regard to the Twenty-Seventh Division, all the information charted is based on cases coming to notice after the arrival of the troops in a distant rest area. A systematic study was performed as outlined in the section entitled "Associated Clinical Observations." Some patients were hospitalized on Saipan and were lost to the present series.
- Despite these defects, the relation of the onset of the ulcers to the conditions of combat is obvious and would doubtless be even more striking were it possible to trace every case. Those ulcers occurring in the Forty-Third Division before the beginning of the New Georgia campaign are examples of the sporadic form of the disease occurring among troops in training or in garrison. The cases in which diphtheritic infection was spread by contact in the Thirty-Ninth General Hospital are not charted.

than twelve weeks' duration contained toxigenic organisms, whereas of 25 older ulcers only 17 (68 per cent) contained toxigenic bacilli. The strains of *C. diphtheriae* obtained by Pasricha and Panja¹² from the extremely chronic ulcers of the Indians of Assam were all atoxic for the guinea pig, and the strains isolated by us from Tonkinese, Melanesian and Chamorro natives were also usually atoxic for the guinea pig. One strain recovered from an ulcer of a patient (Y1) on Nov. 18, 1943 was toxigenic in contrast to one morphologically and biochemically similar obtained on Jan. 28, 1944 from a recurrence. In the Saipan group 2 to 3 colonies from the primary plate were tested in 5 instances to determine whether both toxigenic and atoxic strains might coexist, but the various strains were all toxigenic. In our experience toxigenicity was not lost in vitro when a series of organisms was stored on blood agar for as long as fourteen months with only one intervening transplantation. These observations indicate that the longer *C. diphtheriae* persists in the body the less likely is the recovered strain to be toxigenic. The mechanism of this is not clear, but it probably depends on the formation of atoxic variants.²⁰

The existence of another virulence factor is suggested by an observation of Pasricha and Panja.¹² They found that the nontoxigenic, but otherwise typical, *C. diphtheriae* when injected into the human skin produced ulcers resembling those of the patients from whom the organisms had been obtained, whereas diphtheroids similarly inoculated were totally innocuous. The Schick reactions of their experimental subjects were not stated.

Development and Appearance of the Typical Lesion.—Despite the wide geographic diversity in stations of the various divisions—Solomon Islands, the Marianas, and Philippine Islands—the ulcers observed among these divisions were remarkably similar. They were also similar to the cutaneous diphtheria of the temperate zones, to the “desert” or “Veldt” sores of Libya and Palestine (compare figures in Cameron and Muir⁶), to the “Garigha” of Northern India and to those of the natives and Tonkinese in the New Hebrides and the Chamorros of the Marianas. In the majority of instances the onset of the ulcer was incident to actual combat or patrol activity and was uncommon in resting troops (table 5 and fig. 2). Usually, (in 55 per cent of the cases) there was a definite history of trauma or insect bite (table 6). In such cases the initial lesion, for example a scratch, began enlarging instead of healing. The base, originally linear, became increasingly broad and covered with exudate. The lesion deepened, and the edges, at first red and edematous, became “rolled” as scar tissue formed. Characteristically, granulations failed

20. Dudley, S. F.; May, P. M., and O'Flynn, J. A.: Active Immunization Against Diphtheria, Medical Research Council, Special Report Series, no. 195. London, His Majesty's Stationery Office, 1934.

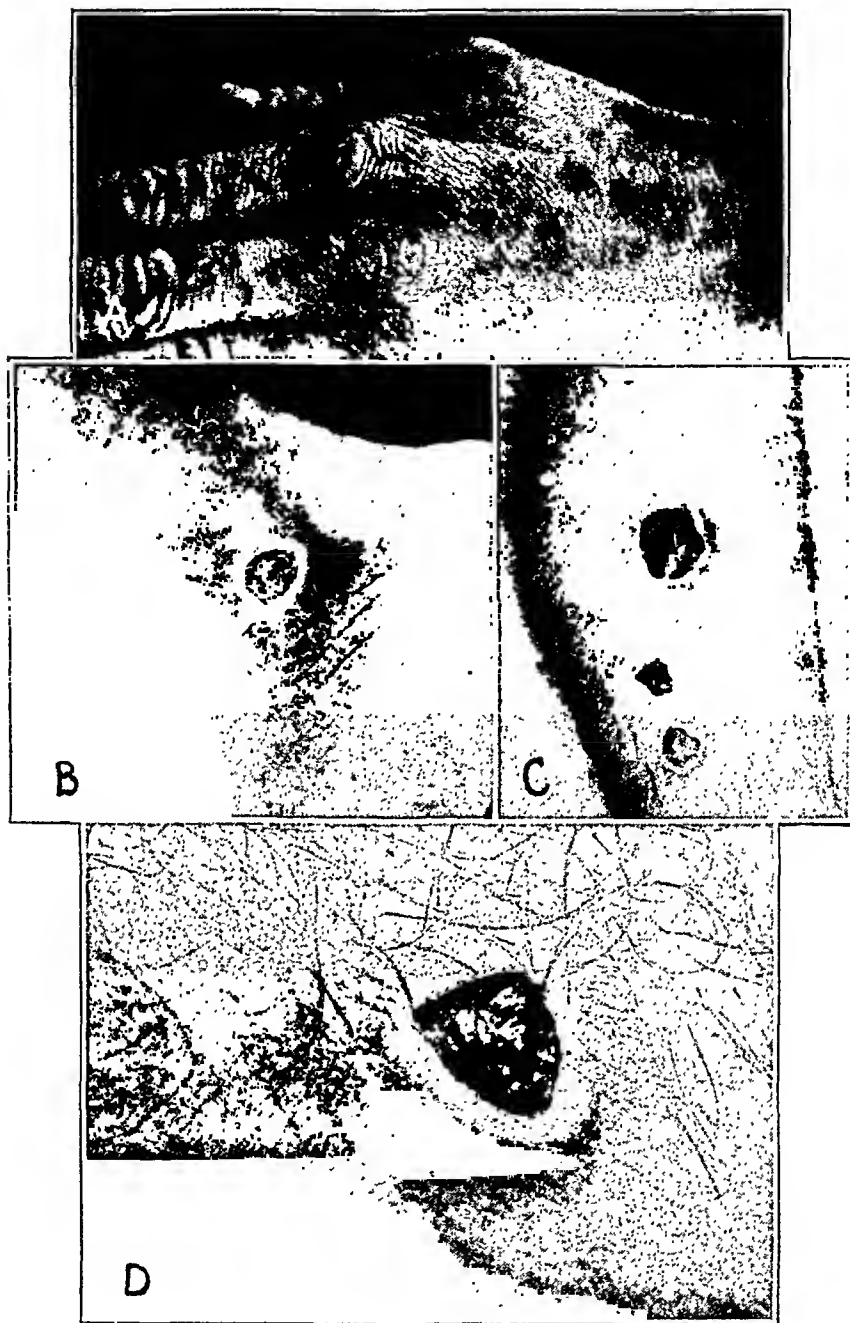


Fig. 3.—All illustrations are of lesions found to contain toxigenic *C. diphtheriae* except as noted in legends. A very high proportion of atypical diphtheritic lesions are illustrated. Those shown in *B*, *C* and *D* and in figure 12 *A* are typical of most diphtheritic ulcers. Patients labeled Y are from the Solomon Islands. Those labeled S are from Saipan. *A* (patient Y52), lesion appears insignificant, but there is deep penetration beneath the scab. Toxigenic *C. diphtheriae* was grown from the exudate.

B (patient Y40), typical chronic ulcer, of four weeks' duration. There is bronze-violaceous pigmentation of the surrounding skin.

C (patient Y43; see fig. 4 *B*), ulcers of leg (photograph of a water color by Private First Class S. L. Abbot).

D (patient S52)), close-up of a typical ulcer of a hand, eight weeks in duration. There is a relatively clean base with only a slight amount of adherent fibrinopurulent material (photograph by United States Army Signal Corps).

to rise but were continuously necrosed at the bottom. Thus the originally linear lesion tended to become rounded or serpiginous, extremely indolent and resistant to treatment in the field.

The diphtheritic lesions were usually multiple (75 per cent) and situated on the extremities (99 per cent). The high incidence of lesions on the feet makes the ulcers frequently disabling. In other locations they are rarely painful and usually cause little inconvenience to the hardy soldier. The lesions varied in size, the largest observed

TABLE 5.—*Islands Where Lesions Were First Noted*

Location	C. Diphtheriae	
	Virulent	Avirulent
Guadalcanal.....	21	8
New Georgia.....	18	4
Vella Lavella.....	5	..
Kolombangara.....	5	..
In transit to or at New Zealand.....	9	1
Saipan.....	63	10
In transit to or at the New Hebrides *.....	14	3

Incidence on the various islands obviously is governed in part by military movements.

There were also 8 patients, not included in the general series, in whom there developed proved diphtheritic ulcers of typical appearance on Leyte.

* One patient from the Forty-Third Division; others from the Twenty-Seventh Division.

TABLE 6.—*Mode of Onset*

Lesion	C. Diphtheriae	
	Virulent	Avirulent
Following trauma or insect bites.....	66	23
De novo.....	30	1
As "small pimples".....	14	1
In diffuse dermatitis.....	4	..
In preexisting epidermophytosis.....	4	1
As "blisters".....	3	1
As pustules.....	2	..
As paronychia.....	2	..
Post fellationem.....	1	..
Total.....	126	27

by us measuring 45 by 40 mm. (case S12). Occasionally a very minute, but otherwise typical, lesion was found to be diphtheritic (fig. 3A).

The characteristic lesions were rounded, deep and "punched out" but did not extend into the subcutaneous tissue (fig. 3B, C and D). Of the lesions harboring *C. diphtheriae* 84.1 per cent had this appearance. The margins were declivitous, indurated and often "rolled." Occasionally they were slightly undermined. Usually there was a zone of induration, erythema and violaceous pigmentation about the sharply defined sore (fig. 3B). The base was usually relatively clean, but sometimes it had some adherent soft fibrinopurulent material or a dried fibrinous crust. The exudate beneath the crust was gray or

gray-green rather than yellow. Occasionally there was a gray-green fibrinous membrane that was impossible to scrape from the surface (fig. 4).

Atypical Lesions.—In 4 instances in which the condition developed in preexisting epidermophytosis of the feet the lesion became a deeply penetrating narrow tract with thick everted lips (fig. 5), resembling those of the cutaneous ulcers seen elsewhere. In 1 case the opening of such a deep tract was minute. It exuded gray seropurulent material and was the source of discomfort entirely disproportionate to its size.

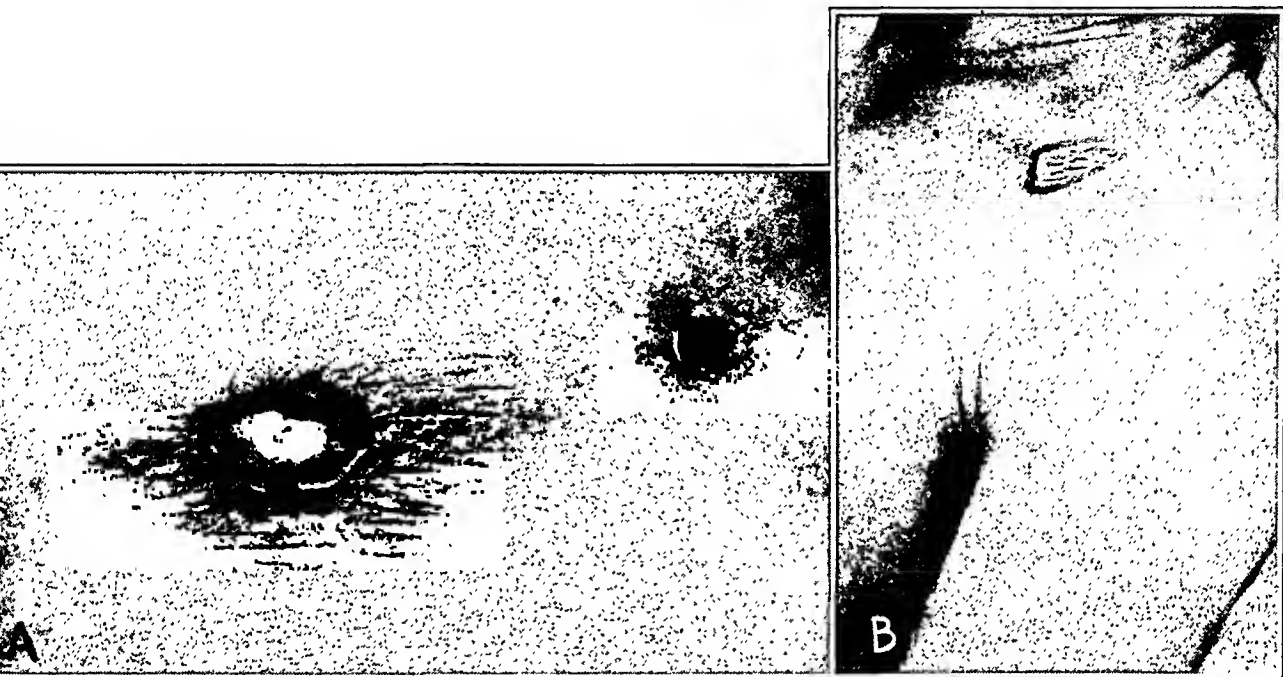


Fig. 4.—*A* (patient S25), diphtheritic ulcer in skin over the left iliac crest, three weeks after onset. It is a relatively shallow but punched-out lesion, with an adherent gray-green membrane at the base.

B (patient Y43), ulcer of skin over the clavicle, with adherent green membrane (photograph of a water color by Private First Class S. L. Abbot).

Any unexplained sinus tract of the feet in soldiers evacuated from the tropics should be suspected of being of diphtheritic origin.

Occasionally *C. diphtheriae* was demonstrated in shallow ulcers or in impetiginous dermatitis (table 4). In 4 instances there was a diffuse moist desquamative and ulcerative dermatitis (fig. 6). One of these (fig. 7 *A*) had multiple paronychias. A wardman attending a patient with diffuse diphtheritic dermatitis had an extremely chronic diphtheritic paronychia of two fingers (fig. 7 *B*).

Some of the shallow ulcers had relatively short histories (fig. 8) and may represent a relatively "acute" stage of the diphtheritic ulcer.

Nevertheless, characteristic deep ulcers can develop in as short a time as one month. This is illustrated by case Y40 (fig. 3 B).

Occasionally the lesions were unusual in location, as in the penis (fig. 9) or in the perianal region (fig. 10).



Fig. 5 (patient S11).—Epidermophytosis superinfected with *C. diphtheriae*. The indurated rolled edge and the deep cavity are characteristic of diphtheritic ulcers in this region.



Fig. 6 (patient Y65).—Moist desquamative and ulcerative dermatitis. Virulent *C. diphtheriae* was isolated from the scalp and from ulcers of a leg.

Relationship of Bacteriologic and Morphologic Findings.—With regard to only those lesions which actually contained toxigenic *C. diphtheriae* (table 4), 118 of 141 (84 per cent) had the typical punched-out character as described in the preceding section. Sixty-eight per cent of the lesions containing atoxic *C. diphtheriae* had this appearance.

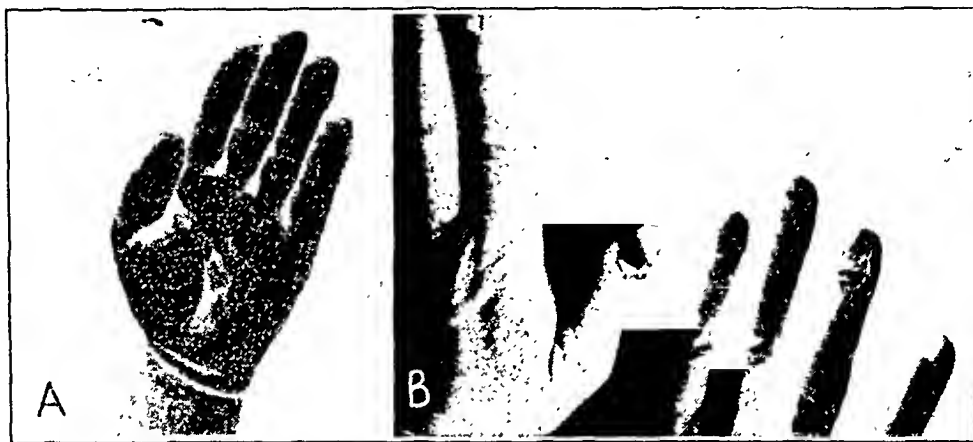


Fig. 7.—*A* (patient Y5), moist desquamative dermatitis of the upper extremities with ulcers of the legs. Note multiple paronychias. *C. diphtheriae* was present in the skin of the palms and in the paronychias. The duration was six weeks.

B (patient Y20), diphtheritic paronychias. Patient was a wardman who took care of an officer (Y68) with a lesion resembling that shown in figure 6.



Fig. 8 (patient Y21).—Crusts adherent to acute relatively superficial ulcers. See section on complications, group A, in text, for details of the history.

With regard to the Saipan group an attempt was made to predict from the clinical appearance of the lesion, before the results of culture

became available, whether or not it would contain *C. diphtheriae*. A correct prediction of whether or not the ulcer would be found to harbor the *C. diphtheriae* was made in 69.1 per cent of attempts at judging 191 ulcerative lesions.

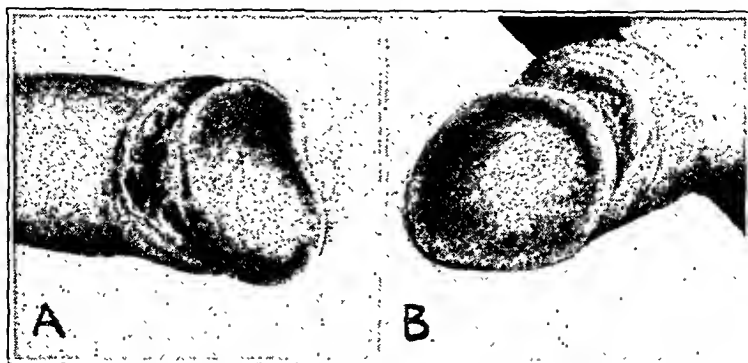


Fig. 9.—*A* (patient Y53), acute diphtheria of coronal sulcus, beginning four days post fellationem.

B (patient Y6), lesion resembling chancre in its firmness but with an adherent green membrane at its base from which virulent *C. diphtheriae* was isolated. The patient had just returned from the tropics and had not had sexual intercourse for more than one year (photographs of water colors by Private First Class S. L. Abbot).



Fig. 10 (patient Y29).—Ulcer resembling a pilonidal sinus. Note kissing ulcer at the right. *C. diphtheriae* was isolated from ulcer of the ankle on Oct. 8, 1943. The patient had diphtheritic neuritis, and spinal fluid proteins totaled 93, mg. per hundred cubic centimeters on December 27.

This suggests that in the age group concerned and in the territory under consideration it is *C. diphtheriae* that plays the important role

in giving the lesions their characteristic morphologic stamp, although no claim is made that the lesion is pathognomonic.

C. diphtheriae is not always found in lesions considered typical (fig. 11). In the Saipan group 98 of 191 ulcers were thought clinically to be typical but only 52 (53 per cent) of the 98 actually yielded *C. diphtheriae* on culture. One explanation is that *C. diphtheriae* has, in time, been replaced by other organisms. This possibility is supported by the data in table 2, as discussed previously. An analogous statement may be that the shovel which dug the ditch is no longer there.



Fig. 11 (patient M.).—Typical ulcers, much treated and partly healed. No *C. diphtheriae* was isolated (two attempts). The patient had diphtheritic neuritis (spinal fluid proteins, 170 mg. per hundred cubic centimeters on Nov. 17, 1943). Tachycardia was noted with changes in the electrocardiogram.

ASSOCIATED CLINICAL OBSERVATIONS

Distant Effects.—Despite the frequent presence of the beta hemolytic streptococcus (table 3), it was remarkable that lymphangitis and lymphadenitis were noted in only 2 patients.

Aside from the occasional presence of neuritis there were usually no general symptoms of intoxication where the ulcers alone were the seat of *C. diphtheriae*. In rare instances there was unexplained tachycardia. One of the patients (Y56; figs. 12 and 13) had a persistent elevation of the pulse rate, on occasion as high as 120, on complete rest in bed without fever or changes in the electrocardiogram. The tachycardia disappeared as the ulcers healed.

In 2 patients with positive Schick reactions a striking erythema and edema occurred about the ulcers on the day following the administration of diphtheria antitoxin. This may be analogous to the Francis reaction as observed in pneumococcal infections.

Relation to the Schick Reaction.—The relation of the incidence of the lesion to the Schick reaction of the person is of considerable interest, as it may have bearing on prevention. Bensted,¹⁵ during the outbreak of diphtheria in British troops in Northwest India, performed Schick tests on members of his battalion. After this he observed that all those in whom diphtheritic ulcers developed had positive Schick reactions. Both the faucial and the cutaneous lesions ceased with the development of immunity following the administration of diphtheria toxoid-antitoxin floccules.²¹ These observations are insufficient in scope to indicate that the skin of a person who does not react to the Schick test cannot become infected with *C. diphtheriae*. In the case of the Twenty-Seventh Division the Schick test was performed on a considerable number of persons during their stay in the rest area. In 1 instance a state in which no reaction could be observed with the test was known to antedate the development of a diphtheritic ulcer. The patient

TABLE 7.—*Schick Reactions of Persons with Diphtheritic Tropical Ulcers*

Group	Patients with				Per Cent Positive Reactors in Division
	Ulcers Containing Toxigenic C. Diphtheriae		Ulcers Containing Atoxic C. Diphtheriae		
	Number Tested	Per Cent Positive	Number Tested	Per Cent Positive	
Thirty-Ninth General Hospital	57	42.1	14	28.5	25th Division, 21% of 9,000 men; 43d Division 27.8% of 11,968 men
Twenty-Seventh Division.....	74	20.3	12	8.5	11.0% of 12,135 men

had been tested one month before admission, and the ulcer was of two weeks' duration. An isolated instance is, however, insufficient to establish the point because of the possibility of error. The most significant evidence that the Schick reaction has bearing on the development of the ulcers is that the percentage of patients with diphtheritic ulcers who react positively to the test is approximately twice that of persons who react positively in the group as a whole (table 7).

The existence of a state in which no positive Schick reaction can be obtained in persons with diphtheritic ulcers can be interpreted to mean either that the organisms resident in the skin have produced immunity or that the ulcers developed in persons in whom a positive Schick reaction was not obtainable. The question of whether the skin of a person who does not react to the Schick test can become infected will not be solved until a sufficiently large number of persons with known

21. Diphtheria toxoid-antitoxin floccules is prepared by treating the filtrate with formaldehyde and then proceeding as for toxin-antitoxin floccules which is prepared by adding diphtheria antitoxin to the filtrate in the proportion necessary to produce suitable flocculation separating the floccules and washing and suspending them in isotonic solution of sodium chloride.

Schick reactions have been studied. This information may be forthcoming by examination of the case records of the men who have already been tested before entering combat in the tropics.

Certain patients have positive Schick reactions despite the fact that ulcers containing toxigenic *C. diphtheriae* have existed for many months. This suggests that the skin is not a good absorbing surface for the toxin. However, with respect to pharyngeal diphtheria it has been long known that a single attack fails to reverse the Schick reaction in about 60 per cent of patients as tested three to four months after recovery.²² Further evidence that the skin does not absorb toxin as well as the pharynx is the long latent period before neuritis developed in the patients whose lesions were purely cutaneous.

The Schick reactions of persons with peripheral neuritis and the relation to therapy are discussed in a later section.

Cutaneous and Extracutaneous Diphtheria in the Same Person.—Previous observers have noted the occasional concomitance of cutaneous and extracutaneous diphtheria (table 8). Routine cultures of material

TABLE 8.—*Corynebacterium Diphtheriae* Occurring Concomitantly in the Skin and Elsewhere in the Same Persons

Reference	Number of Ulcers	Patients			Carriers		
		Faucial	Nasal	Faucial and Nasal	Faucial	Nasal	Faucial and Nasal
Bensted ¹⁵	31	2
Cameron and Muir ¹⁶	66	8	4	3	3	4	3

from the noses and the throats of the 174 patients with diphtheritic ulcers have demonstrated *C. diphtheriae* in 19 of them: Ten of these clinically had pharyngeal diphtheria and 2 fibrinous rhinitis. There were also 6 pharyngeal carriers, and 1 was a nasal carrier.

The 12 clinical cases are of particular interest. In 3 of them the patients (Y8, Y27 and Y28) had been sent to the hospital for the treatment of the ulcers and were found to have positive Schick reactions at the time of admission. The acute pharyngitis developed while the patients were in strict isolation for periods varying from two and a half to five weeks. In all 3 cultures of material from the throat were negative for *C. diphtheriae*, and the patients did not receive antitoxin until pharyngitis became manifest. These cases demonstrate that in all probability autoinfection of the nasopharynx from the skin can occur.

In the other clinical cases the patients were admitted primarily for the pharyngitis or rhinitis, although in 5 of them the ulcers antedated the diphtheria of the throat for periods varying from three to seven weeks.

22. Dudley, S. F.: Critical Review: Schick's Test and Its Applications, Quart. J. Med. 22:321-379, 1929.

Neuritic Complications.—Many patients with peripheral neuritis and pharyngeal and ocular palsy have been seen in military hospitals serving the Pacific area. Some of these have been associated with clinically recognized and bacteriologically confirmed nasopharyngeal diphtheria. Many writers, including Norris, Kern, Schenck and Silcox,²³ have commented on the great frequency of neuritis as a complication of diphtheria in the tropics, despite the mildness of nasopharyngitis. Perhaps it is the mildness which accounts for the apparently high incidence of neuritis; i. e., many cases are so mild that they are probably dismissed as cases of ordinary nasopharyngitis, unless routine cultures are taken. This has been our experience as

TABLE 9.—*Neurologic Complications in Patients Proved to Have Cutaneous Diphtheria*

Reference	Total No. of Patients with Ulcers	No. with Neurologic Complications	Nature of Complication			Comment
			Paralysis of Accommodation	Paralysis of Pharynx	Peripheral Neuritis *	
Cameron and Muir ⁶	66	5 without <i>C. diphtheriae</i> elsewhere	5	
		7 with <i>C. diphtheriae</i> in skin and elsewhere	1	2	6	
Bensted ¹⁵	31	3	3	One patient with lesion on face had facial neuritis
Walshe ⁵	30 (selected group)	..	10	..	30	No report of culture of nose and throat
Fleck, Kellam and Klippen ⁹	4	1	1	Patient also had myocarditis
Present report.....	174†	3	3	See table 10

* Peripheral neuritis includes sensory, motor and reflex manifestations.

† The follow-up data were incomplete for reasons explained in the text: (a) The 89 patients from the Salpan group (Twenty-Seventh Division) were not to the time of writing followed long enough for neuritis to occur; (b) the careful successive physical examinations necessary to detect minor signs of peripheral neuritis could not be performed even in the majority of the other instances for military reasons of transfer to other areas and for other reasons.

well as that of others.⁹ The mildness of the nasopharyngeal disease in the face of the high incidence of neuritic complications is difficult to explain. The possibility that tropical strains of *C. diphtheriae* may be different from those of temperate climates should be investigated. A more likely explanation is based on Dudley's²⁰ theory of "latent immunization"—that owing to its widespread dissemination among troops in the tropics *C. diphtheriae* has raised the concentration of antitoxin in the blood of some persons to a level higher than that in

23. Norris, R. F.; Kern, R. A.; Schenck, H. P., and Silcox, L. E.: Diphtheria in the Tropics: A Report of Eighteen Cases on a United States Naval Hospital Ship, U. S. Nav. M. Bull. 42:518-524, 1944.

the unexposed but not enough to reverse the Schick reaction or to prevent the absorption of toxin to an extent sufficient to result in neuritis. Only detailed correlated studies of serum levels of antitoxin can adequately put the latter hypothesis to the test.

Neuritis has also been noted in cases of cutaneous diphtheria originating in the tropics (table 9). Some of these⁵ are particularly difficult to evaluate, since there is no record of an attempt to rule out the existence of *C. diphtheriae* in the nose and the throat. The material encountered by us can be subdivided as follows:

Group A: Neuritis complicating proved cutaneous diphtheria without evidence of *C. diphtheriae* elsewhere.

Group B: Neuritis associated with ulcers of the skin unhealed at the time of admission but not demonstrated to contain *C. diphtheriae*.

Group C: Neuritis in persons with scars of tropical ulcers.

Group D: Neuritis in persons with scars of tropical ulcers and history of sore throats.

Group E: Neuritis in persons proved to have diphtheritic pharyngitis.

Group F: Other cases of neuritis clinically indistinguishable from diphtheritic neuritis.

Group A: In table 10 are summarized the salient clinical features of the 3 patients in the present series in whose ulcers toxigenic *C. diphtheriae* was actually demonstrated. The patients are all derived from the group of 85 patients with ulcers seen in the Thirty-Ninth General Hospital. Most of those in the Saipan group were not observed for a sufficiently long period to the time of writing for neuritis to have developed. None of these men had a history of sore throats, nor did routine cultures of material from the nose and the throat yield these organisms. In these 3 patients the symptoms began between three and seven months after the lesion was first noted by the patient. In 2 of them the lesion occurred two and four months respectively after the time that the virulent *C. diphtheriae* was first isolated from the lesions. In pharyngeal diphtheria (group E) the neuritis most commonly begins within six weeks after onset.²⁴

Unlike the nature of the complications following pharyngeal diphtheria, the cranial nerves were not involved in cases in which the lesions proved to be purely cutaneous. A glance at table 9 will show that this has been true also of previously reported series. Obviously, it is difficult to be certain in any instance that the organisms had never been present in the nose or the pharynx, but the clinical differences in the manifesta-

24. Cecil, R. L.: *A Text-Book of Medicine*, Philadelphia, W. B. Saunders Company, 1935.

TABLE 10.—*Neuritis in Patients with Tropical Ulcers*

Patient	Date of Onset and Healing of Ulcers	Date Admitted to Hospital and Lesions Observed	Result of Schick Test	Treatment	Apparent Date of Onset of Neuritis and Symptoms	Spinal Fluid Examination Results	Cultures of Material from Nose and Throat
				Group A			
Y21*	July 1943; healed 11/19/43; recurred 12/15/43; healed 2/14/44	10/10/43; multiple typical ulcers of buttocks and ankles	+ (10/31/43) — (1/3/44)	40,000 units D.A.T.† (11/1/43); saline soaks	2/20/44; numbness in feet; hypesthesia from ankles down; difficulty in standing on toes	Protein 105 mg. % (2/20/44); 125 mg. % (4/24/44)	Negative (10/28/44 and 11/16/44); later also negative
Y25	May 1943; healed 10/11/43	8/30/43; typical ulcers of feet	— (9/1/43)	20,000 units D.A.T. (9/6/43); saline soaks	10/20/43; numbness beginning in hands and then involving feet; "glove and sock" hypesthesia; hyporeflexia of right leg	Protein 68 mg. % (10/30/43)	Negative (9/1/43)
Y29	November 1942; healed?; recurred July 1943; healed 11/20/43	10/9/43; typical ulcers of elbows, ankles, postcoecogecal region (fig. 10)	— (10/12/43)	Saline soaks; no D.A.T.	10/20/43; paresthesia in fingers and toes	Protein 68 mg. %; colloidal gold curve 543333000 (10/25/43)	Negative (10/12/43 and 11/16/43)
M†	July 1943	9/2/43; typical ulcers of feet (fig. 11)	— (9/1/43)	No D.A.T.	9/10/43; paresis of accommodation	170 mg. % (11/17/43)	Negative (9/13/43)
B	September 1943; healed 12/18/43	11/18/43; typical ulcers of legs and feet	— (date not recorded)	No D.A.T.	12/27/43; numbness of feet; plantar hypesthesia; diminished deep reflexes	Pandy reaction 2+; colloidal gold curve 0000000000 (3/14/44)	None recorded
D	8/10/43; healed?	1/4/44; scars of calves and toes	+ (1/5/44)	No D.A.T.	End of Sept. 1943; paresthesia and weakness of calves; hypesthesia and diminished vibration sense of legs; absent deep reflexes	Protein 85 mg. % (1/8/44)	Negative (1/5/44)
N	July 1943; healed September 1943	November 1943; scars on all four extremities and of buttocks	— (Nov. 1943)	No D.A.T.	One week after onset; numbness in fingers and toes; slight difficulty in swallowing; general weakness; hypesthesia of legs	Protein 39 mg. % (Nov. 1943)	Negative (Nov. 1943)
W	Sore throat 8/7/43; ulcers a few days later	10/7/43; scars on right hand, left finger and right leg	+ (10/8/43)	No D.A.T.	Sept. 5; transient difficulty in swallowing; Sept. 12; weakness and paresthesia; hypesthesia, "glove and sock"; deep reflexes of legs absent	Not examined	Negative (Oct. 1943)
Bj	Ulcers Feb. 1943; others and sore throat Sept. 1943; healed Nov. 1943	1/8/44; scars of legs and hands	— (1/9/44)	No D.A.T.	Late October; blurring of vision; end of Nov. 1943; numbness in extremities; muscular weakness; loss of deep reflexes; hypesthesia and loss of vibration and position sense	Protein 68 mg. % (1/17/44); 53 mg. % (2/22/44); colloidal gold curve 0000000000	None recorded
P	8/10/44; ulcers healed?; indefinite history of occlusional sore throats	12/29/43; scars of neck, arms and legs	— (1/15/44)	No D.A.T.	Late November; blurring of vision (transient); Jan.; weakness; hypesthesia; loss of proprioceptive sense and deep reflexes	Protein 81 mg. %; colloidal gold curve 0011100000 (1/19/44); 36 mg. % (3/10/44)	Negative (1/17/44)
S	May 1943; ulcerative dermatitis of heels; repeated sore throats and tonsillitis	12/6/43; scars of heel	Not recorded	No D.A.T.	12/3/43; hypesthesia distal parts of all extremities, thorax and abdomen	Protein 68 mg. % (12/11/43)	None recorded

* The patient was not discharged from hospital in the United States until October 1944.
† Patient had tachycardia. Changes in electrocardiogram (Sept. 11, 1943), gradually resolving by Dec. 20, 1943.

tions of the neuritis suggest that the pathogenesis of the lesion may actually be the production of toxin by the organisms in their cutaneous location.

The first symptoms of neuritis in the cases in which the lesions are purely cutaneous are usually those of paresthesia followed by weakness of the extremities. The observations on physical examination may be minimal and are usually those of hypesthesia to pinprick and light touch. The deep reflexes are usually diminished or totally absent. Position sense is altered in some instances.

Elevation of protein in the spinal fluid, as is to be expected in any form of neuritis, is present at some time in almost all these patients. It is a valuable observation in that it affords evidence that the patient is not malingering. In no instance has there been pleocytosis, although this condition has been recorded by some,³ but occasionally changes in the colloidal gold curve occur (see patients Y29 and P in table 10). The long persistence of the elevation of the protein in the spinal fluid is demonstrated in some of these records.

Groups B, C and D: The symptoms, signs and laboratory observations are similar to those of group A, except that *C. diphtheriae* was not demonstrated. The long interval of time elapsing between the onset or even the healing of the lesion and the appearance of the neuritis has been noted by others.

Although the history of sore throat from some of the patients in group D is indefinite, this factor must be given great consideration despite the presence of the scars of the ulcers. It is notable that 2 of these patients had evidence of cranial nerve palsies.

Group E: There were 4 patients among the group of 34 patients with nasal or faucial diphtheria in the Thirty-Ninth General Hospital and 3 among the 37 patients from the Twenty-Seventh Division in whom neuritis developed during the six weeks of our observation. One of the former group (Y42) had diphtheritic ulcers of the skin as well as unilateral diphtheritic rhinitis at the time of admission.

In most instances the neuritis developed approximately six weeks after the onset of the sore throat. It is notable that 5 of the 7 patients had cranial nerve palsy manifested by difficulty in swallowing with regurgitation of the food through the nose. In 6 of the 7 there was peripheral neuritis of the same sort observed in the other groups. The spinal fluid of 2 patients was examined and showed total protein elevated to 58 mg. and 170 mg. per hundred cubic centimeters, respectively.

Group F: Shortly after the opening of the Thirty-Ninth General Hospital 6 patients with neuritis were transferred from a naval hospital. The records of these are no longer available. Their conditions were suspected to be of diphtheritic causation, but proof was lacking.

Since the diphtheritic nature of certain tropical ulcers became apparent, there has not been an instance in which neuritis of the type discussed in the foregoing paragraphs could not be related to the ulcers, to sore throats or to proved diphtheritic pharyngitis or dermatitis.

Treatment.—After the diphtheritic nature of certain tropical ulcers was recognized, all ulcers at the time of the patient's admission to the hospital were treated as dangerous wounds. When *C. diphtheriae* was demonstrated, the patients were isolated. In handling outpatients, especially with regard to the Twenty-Seventh Division, a centrally located clinic was established to which all patients with ulcers were referred for cultures. Patients found to have *C. diphtheriae* were admitted to the hospital. In this way the patients were placed under treatment, and a curb was put on dissemination of the organisms.

Tables 11 and 12 summarize data concerning various factors in therapy. The most important principle in promoting healing of the ulcers seems, in our experience, to be rest in bed and the application of moist dressings. If the patients are treated as outpatients in the usual

TABLE 11.—*Relation of Toxigenicity of C. Diphtheriae to Healing Time in Hospital*

	Number of Patients	Mean \bar{g} Healing Time, Days
Organisms toxigenic.....	107	19.2
Organisms atoxic.....	21	11.4

"Healing Time" does not refer to total days of hospitalization, nor does it refer to total time of existence of ulcer.

Mean \bar{g} is the geometric mean.

fashion with a paste containing a sulfonamide compound and dry dressings, the lesions remain unhealed for many weeks and the patients continue to be a prolific source of diphtheria bacilli.

Ulcers containing atoxic organisms tend to heal more rapidly under hospital treatment (table 11) than those containing toxigenic organisms.

A relatively high level of antitoxin in the patient's blood as indicated by absence of reaction to the Schick test also seems to favor healing, although there are, as yet, insufficient data to prove this statement statistically. Serum therapy of chronic ulcers in persons with positive Schick reactions has not in our hands been productive of remarkable results, although some writers²⁵ have recommended the use of small doses of serum. Certainly serum is not lethal to the organisms, which may persist for many days after the treatment. One patient (Y43) had the organisms in the lesion five days after the intramuscular administration of 20,000 units. Antitoxin, however, acts as a prophylactic in preventing the serious consequences of autoinfection

25. Manson-Bahr, P.: The Prevalent Diseases of Libya, *Lancet* 1:253-255, 1941. Bensted.¹⁵ Cameron and Muir.⁶ Craig.⁴

of the nose and the throat. After several examples of this had been observed, antitoxin was given to almost all the patients with positive Schick reactions. Antitoxin did not prevent the subsequent development of neuritis when given late, even during the course of a cutaneous infection (table 10, group A). That serum administered to patients with nasopharyngeal infection to prevent this complication is ineffectual when given after the third day has been stressed in Rolleston's³ table.

When penicillin became available, observations were made to determine its effect. From a comparison of groups 1 and 7 in table 12, it seems that the actual healing time is shortened by two days at the most. Nevertheless, penicillin locally applied in concentrations of 250 units per cubic centimeter of saline solution gave certain definite indications of efficacy. This became evident during the course of a

TABLE 12.—*Lesions Containing Toxigenic C. Diphtheriae; Relation of Type of Treatment to Healing Time in Hospital*

Group Number	Treatment	Result of Schick Test	Mean Healing Time, Days	Number of Patients
1	Local *	—	18.6	27
2	Local	+	59.0	1
3	Antitoxin	—	43.3	3
4	Antitoxin	+	25.2	20
5	Antitoxin and penicillin	—	7.4	3
6	Antitoxin and penicillin	+	18.0	6
7	Penicillin	—	16.5	43
8	Penicillin	+	14.1	3

* Local treatment excluded penicillin applications.

series of controlled observations on patients who failed to react to the Schick test and whose lesions contained toxigenic bacilli. The lesions of 1 of these patients are illustrated by figures 12 and 13 and are described in the legend of figure 12. The lesions on the right leg, which were subjected to the local as well as the systemic effects of the penicillin, assumed a healthy granulating appearance sooner than the others. In them, although they were larger and had more adherent necrotic material than the others, *C. diphtheriae* had disappeared after forty-eight hours of treatment, whereas in one of those on the left leg the organisms persisted until the fifth day. Under the influence of penicillin locally applied the bacterial flora gradually changed after the second day so that gram-negative bacilli, especially *Bacillus pyocyaneus* and *Alcaligenes faecalis*, came to replace the gram-positive bacilli and cocci which predominated at first. In a series of 5 patients from the Saipan group (S5, S27, S36, S44 and S54) penicillin was not given intramuscularly, but in each instance an ulcer treated locally with penicillin was compared with a control treated with saline solution. In each case the Klebs-Löffler bacilli had disappeared from the lesions forty-eight hours after the application of penicillin, whereas the organ-

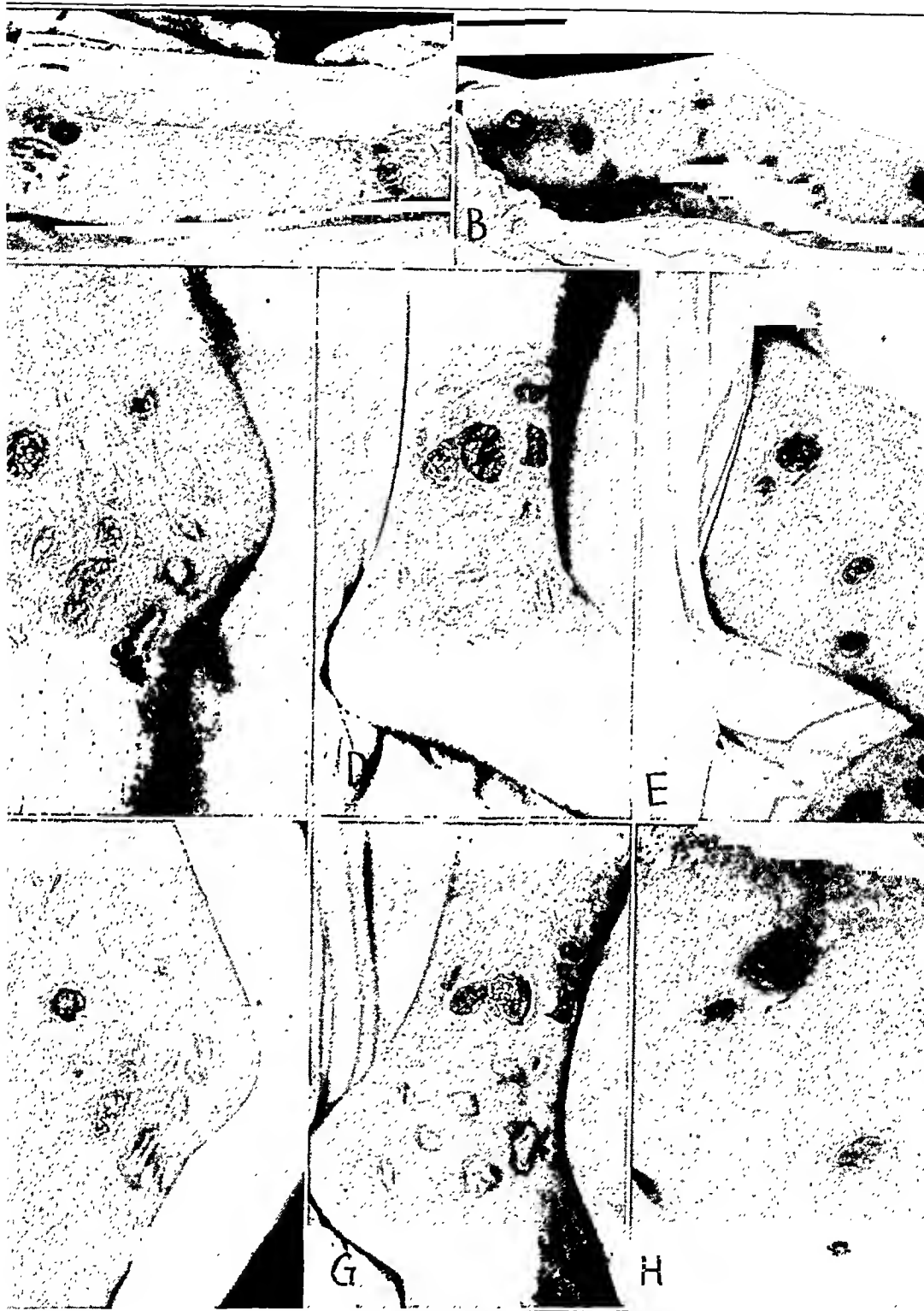


Fig. 12 (patient Y56).—Multiple diphtheritic ulcers of lower extremities. The patient was given 300,000 units of penicillin a day intramuscularly in five doses for eight days. The right leg also received compresses of isotonic solution of sodium chloride containing penicillin (250 units per cubic centimeter) for four hours in the morning and four hours in the afternoon. Soaks of isotonic solution of sodium chloride were applied to the left leg for control at all times and to the right leg in the intervals between the applications of penicillin. The patient showed no reaction to the Schick test at the time of his admission.

A, right leg, May 24, 1944, at the start of treatment.

B, left leg, May 24. *C* and *D*, right leg, May 27, after three days of penicillin locally. *E*, left leg, May 27—control. *F* and *G*, right leg, May 31, after seven days of penicillin. *H*, left leg, May 31—control.



Fig. 13 (patient Y56).—*A* and *B*, right leg, June 10, 1944, after seventeen days of local penicillin therapy.

C, left leg, June 10. Penicillin had been applied as in the case of the right leg, beginning June 6.

D and *E*, general view, comparable to *A* and *B* of figure 12, June 26. The lesions are almost healed.

F, *G* and *H*, close-ups, comparable to *C*, *D* and *E* of figure 12, June 26. Note the development of bronze pigmentation.

isms were at that time still present in the ulcers treated with the simple pack of saline solution. Gram-negative flora was again predominant where the exudate had been in contact with the penicillin. An examination of 1 patient with a positive Schick reaction (Y57; fig. 14) showed a similar disappearance of *C. diphtheriae* within forty-eight hours and a like change in the flora.

The removal of *C. diphtheriae* is obviously desirable both in reducing the danger of neuritis and in lessening the epidemiologic hazard. Further information is necessary concerning this point. It is

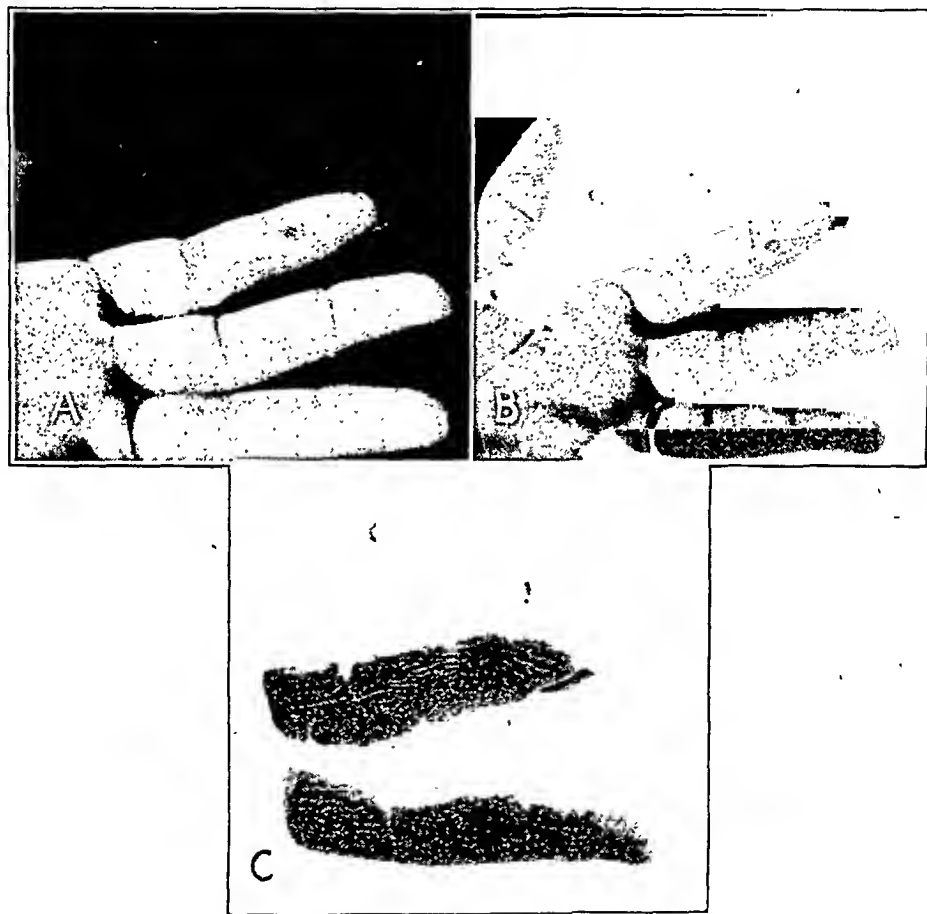


Fig. 14 (patient Y57).—*A*, diphtheritic ulcer of one month's duration. There was no history of injury. The patient had a positive Schick reaction.

B, after six days of treatment with penicillin.

C, after nineteen days of treatment with penicillin.

important also to culture material from the nose and the throat before the patient is released from isolation.

Although *C. diphtheriae* is sensitive to sulfonamide compounds *in vitro*, it seems to be almost unaffected by these drugs when present in the ulcers. In many instances the organisms were isolated directly from lesions packed with crystals or covered with ointments containing

sulfonamide compounds. This is confirmed clinically by the fact that many of these same outpatients had been thus treated for months before the cultures were made, with slow, if any, improvement or occasional progression, of the lesions. Applications of sulfonamide compounds give the lesions a cleaner appearance.

In a few cases special measures have been taken. Among these is the application of casts to secure immobilization where this has been difficult to obtain by other means. Excision of the lesion has been practiced in one very unresponsive ulcer, with primary healing of the wound. This may shorten the period of hospitalization in particular instances. Skin grafts have been applied to the bases of some large ulcers after they began to granulate cleanly, but these grafts usually fail to take.

EPIDEMIOLOGIC SIGNIFICANCE OF CUTANEOUS DIPHTHERIA

Evidence Gathered from Contacts in Thirty-Ninth General Hospital.—Considerable evidence has accrued that cutaneous diphtheria, particularly when unrecognized, is important in spreading the bacilli not only to the skins but also to the noses and the throats of others. This was most clearly demonstrated when infection apparently the result of contact developed in 7 persons in the Thirty-Ninth General Hospital, 6 among ward personnel and 1 among the patients, before tropical ulcers were recognized to be diphtheritic. A nurse caring for an officer (patient Y68) with widespread desquamative and ulcerative lesions, resembling those in patient Y65 (fig. 6), had a paronychia and an abscess in her arm from which *C. diphtheriae* and beta hemolytic streptococci were isolated. Another nurse caring for the same patient had a sore throat, which was not of the membranous type. This nurse was known to have been negative to the Schick test two years previously. *C. diphtheriae* was isolated from her throat. In another officer, who was admitted for jaundice two weeks previously and who did not have a sore throat at the time of admission, in the cubicle next to that of patient Y68, there developed extensive membranous nasal and pharyngeal diphtheria. In a wardman (Y20, fig. 7 B) in another ward, where many patients with tropical ulcers were kept, there developed a paronychial granulomatous and ulcerative lesion from which the toxigenic corynebacteria were isolated, and shortly thereafter another attendant in the same ward had diphtheritic pharyngitis. A wardman working in another ward for patients with cutaneous diseases, where there were many patients with ulcers, contracted pharyngeal diphtheria.

After the patients with the ulcers were isolated until they proved to be nondiphtheritic, there were no further cases of infection developing as a result of contact except 1 in which a nurse, attendant on an isolated patient with diphtheritic pharyngitis, contracted severe membranous

nasal diphtheria. From all 8 of these patients infected by contact virulent corynebacteria were isolated.

Direct evidence of autoinfection of the pharynx in persons harboring the organisms in the skin is presented in the section entitled "Associated Clinical Observations."

In all reported outbreaks of diphtheritic tropical ulcers among military populations the incidence of ulcers (table 1) has exceeded that of nasopharyngeal diphtheria and carriers. Furthermore, the carrier rate among persons without ulcers may be low. In a study of the carrier rate among 201 men of the Thirty-Fifth Infantry in the Twenty-Fifth Division, only 2 carriers, both with nasal infections and without symptoms, were discovered. Likewise, in the Twenty-Seventh Division,

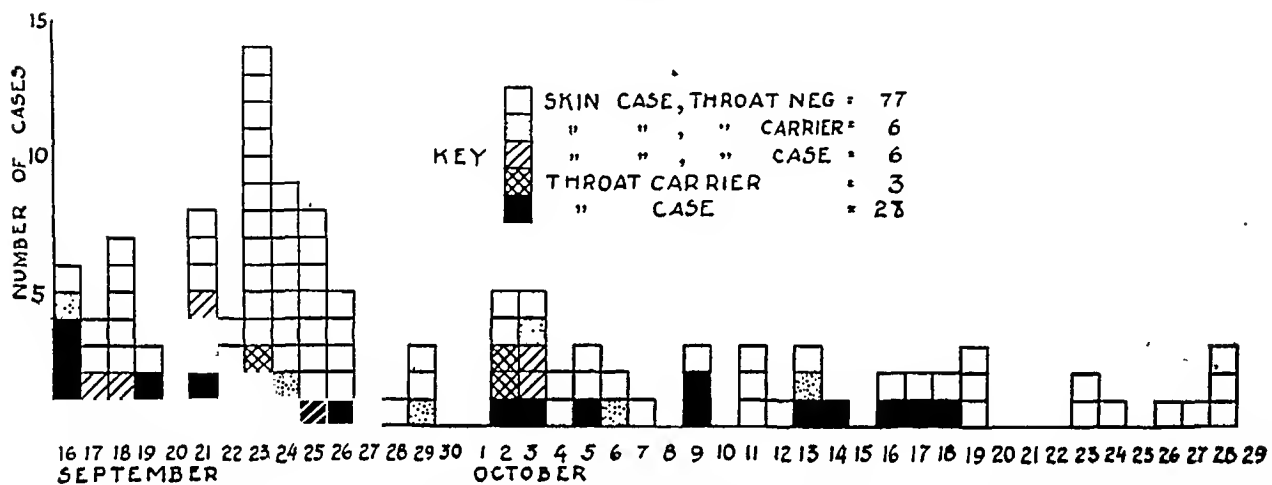


Fig. 15.—Cases of diphtheria in the Twenty-Seventh Division in a rest area. Each block represents 1 case. The date of the patient's admission determines the position of the block, unlike figure 2 in which the date of onset is charted.

The relative infrequency of the cases of extracutaneous diphtheria toward the right of the figure is obvious.

routine study of approximately 600 men resulted in the discovery of only 3 pharyngeal carriers who did not have ulcers of the skin. The total incidence among these 801 then is 0.6 per cent. Among patients with diphtheritic ulcers, however, 7 asymptomatic carriers were discovered in the entire series of 174 patients, an incidence of 4 per cent.

As the patients with ulcers were removed from the division in the rest area, the incidence of nasopharyngeal diphtheritic infection decreased rapidly. The experience in the case of the Twenty-Seventh Division is illustrated in figure 15. It is similar to that with the Twenty-Fifth and Forty-Third Divisions and almost identical with that of Bensted¹⁵ and his troops in Northern India (see his chart).

Possible Relation to Outbreak of Diphtheria in Europe.—Certain correlations suggest that the skin may be the ultimate source of bacilli affecting much larger susceptible populations. During the World War II

there has been a remarkable increase of diphtheria in Europe (fig. 16). It is of great note that this coincided with the beginning of the return of German soldiers of the African Corps to Europe. In this connection the considerable outbreaks of diphtheria among German prisoners

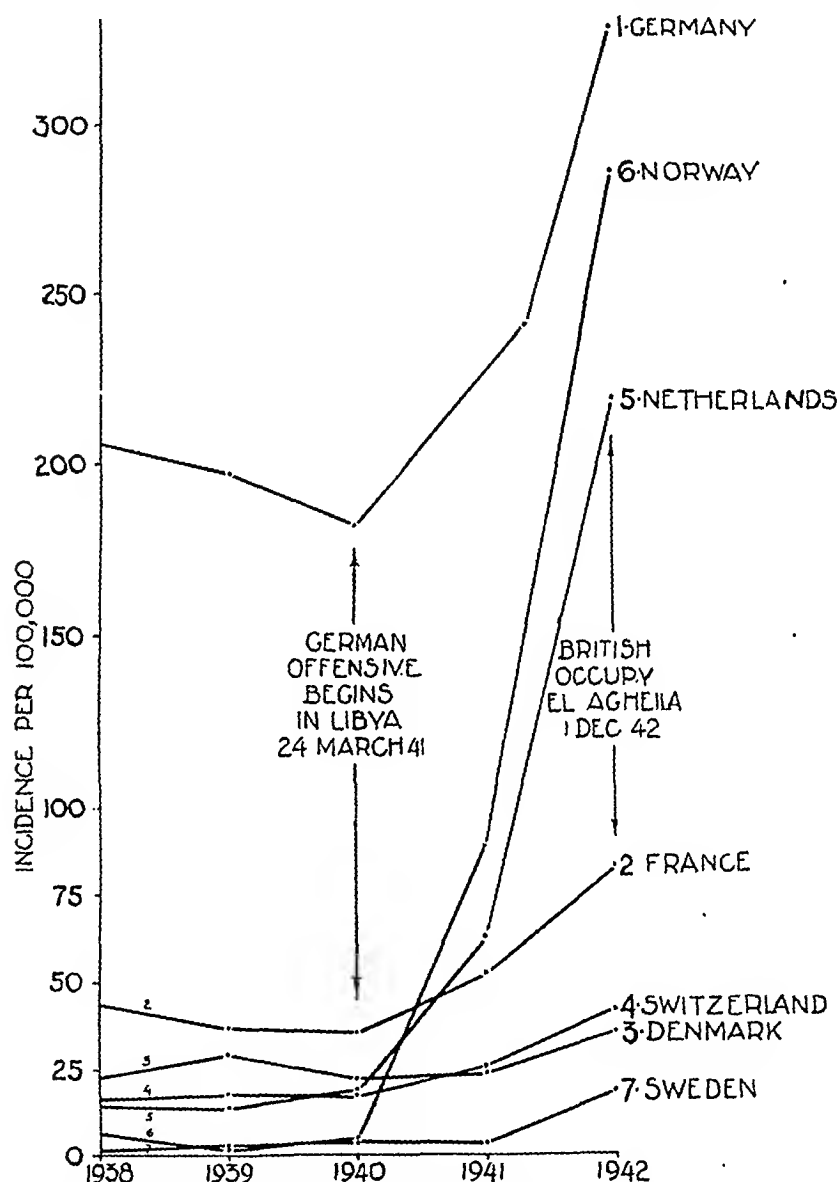


Fig. 16.—Rate of occurrence of diphtheria in European countries from 1938 to 1942, inclusive. The information on which this chart is based was obtained from the data contained in "Diphtheria Susceptibility and Immunization," Bull. U. S. Army M. Dept., 1944, no. 76, pp. 104-108, and in the War Department Technical Bulletins. The statistics of population on which the incidence per hundred thousand is estimated are those contained in "The World Almanac" for 1944.

Incomplete figures for 1943 indicate a continued enormous rise in the incidence in Norway and the Netherlands to more than double that of 1942 in each country.

of war captured in Africa and confined in camps in the United States and Trinidad, British West Indies, must be mentioned. The description of an outbreak in such a camp⁹ is particularly interesting, since

4 of the ulcers, which were said to be numerous, were proved to be diphtheritic. Among Italian prisoners of war, however, there have been no epidemics as far as is known to the writers.

The rise in diphtheria rates during 1941 was most striking in Norway, a country with a previously very low diphtheria rate and where immunization had not been practiced. It may be presumed that German troops were sent to rest in relatively pleasant and inactive areas, such as Norway and the Netherlands. Certainly in the former country the German conqueror was relatively scrupulous; dietary condi-

TABLE 13.—*Incidence of Toxigenic and Nontoxigenic Strains of C. Diphtheriae in Patients with Extracutaneous Diphtheria and in Carriers*
(Thirty-Ninth General Hospital, Feb. 7, 1943 to July 1, 1944)

	Patients			Carriers				
	Throat	Nose and Throat	Nose	Throat	Nose and Throat	Nose	Nose and Sputum	Nose and Ears
<i>C. diphtheriae</i> toxigenic (total, 39).								
No ulcers.....	23	1	3	2	2	1
Cutaneous diphtheria also present	4	..	2	1
<i>C. diphtheriae</i> atoxic (total, 10).....	1	2	1	4	1	1
Total.....	28	1	5	4	3	6	1	1
Grand total of patients and carriers, 49								

tions were relatively good, and there was no necessity for frequent unnatural crowding, as in shelters, to amplify the epidemiogenic opportunities of the Klebs-Löffler bacilli. It is interesting to note that the two neutral countries, Switzerland and Sweden, showed a delayed and slight rise. Recent information indicates that the increase in morbidity from diphtheria in France was largely in the occupied zone. The very slight increase in Austria is difficult to understand, unless this country was out of the line of evacuation from the desert.

In New Zealand—to consider a country remote from the war and well fed—a rise in diphtheria morbidity began in 1942 and continued through 1943 as follows: 1940, 368; 1941, 383; 1942, 642; 1943, 830. Perhaps an explanation is the increment in the concentration of the etiologic agent supplied by marines and soldiers returning from the area of the Solomon Islands.

The diphtheria in the former, whose influx into the country began in 1942, is described by Norris, Kern, Schenck and Silcox.²³ The Twenty-Fifth Division appeared en masse in New Zealand in 1943. Thus the stream of persons infected with *C. diphtheriae* has been uninterrupted until the middle of 1944. The drafts of New Zealand soldiers from Africa did not return to New Zealand until the middle of July 1943, and they were not numerous. The previous peak in New

Zealand was in 1917 and 1918 and may have been associated with the return of soldiers at that time from Gallipoli, Turkey, and the desert.

It is of great interest that in the words of Friederich Löffler,²⁶ "the disease appears to have been perfectly well known in Egypt, Syria and Palestine even in ancient times. This is proved by repeated references to it in the Babylonian Talmud." Also, according to Rolleston,⁸ in the first century A. D. "an unmistakable description of diphtheria is given by Aretaeus of Cappadocia under the name of Syriac or Egyptian ulcers owing to its having originated in Syria and Egypt whence it spread to all European countries." The term "ulcers" refers to the appearance of the throat and not to the skin in this instance.

These correlations are not held up as final proof but are presented for closer analysis when more detailed information becomes available, especially concerning the movements of German soldiers returned from Africa and the Middle East. From the evidence at hand, correlating the intimate observations made within the confines of a hospital concerning the epidemiologic significance of the diphtheritic skin with the larger facts of the concomitance of the cutaneous and pharyngeal forms among troops in widely scattered tropical and desert regions, and the increase in diphtheria in the countries of Europe, the problem assumes significant proportions. As Rolleston says, "subjects of clandestine diphtheria, like clandestine prostitutes, are of considerable epidemiological importance, as both, owing to their innocent appearance, may widely spread disease before their true nature is recognized." Certainly the diphtheritic nature of "tropical ulcers" has not been widely recognized, and their frequently inconsequential appearance has made them particularly dangerous.

GENERAL CONSIDERATION OF DIPHTHERIA IN THE TROPICS

The Native Reservoir.—It is paradoxical that although clinical nasopharyngeal diphtheria is apparently rare among natives there is abundant evidence of the widespread dissemination of *C. diphtheriae* in the tropics in direct contrast to what has been observed in the coldest parts of the world.²⁷ The rarity of nasopharyngeal diphtheria and neuritis was attested by Captain Rutter, British medical officer in the Solomon Islands, Dr. Guépin of the French Colonial Medical Service in Espiritu Santo, New Hebrides, and the Fijian medical practitioner, Asari. Natives of low latitudes generally possess a high degree of immunity as evidenced by absence of reactivity when

26. Nuttall, G. H. F., and Graham-Smith, G. S.: *The Bacteriology of Diphtheria*, London, Cambridge University Press, 1908.

27. Heinbecker, P., and Irvine-Jones, E. I. M.: Susceptibility of Eskimos to the Common Cold and a Study of Their Natural Immunity to Diphtheria, Scarlet Fever and Bacterial Filtrates, *J. Immunol.* 15:395-406, 1928.

given the Schick test. This has been found true of the Filipinos, Malays, Javanese, Hondurans and Brazilians. Among the Bantu of Africa²⁸ the incidence of Schick test immunity increases with age but more rapidly than among Europeans. This problem has recently been made the subject of an extensive study by Murray,²⁹ who compared the Schick test results, the carrier rates and the incidence of clinical diphtheria of rural and urban Bantu natives of Africa. In the 6 to 8 year (inclusive) age group the percentages of persons with positive Schick reactions were 11.8 for the rural and 17.2 for the urban children, and the respective percentages for the 15 to 17 year age group were 5.1 and 12.0. The percentages for white children in South Africa were approximately five times as high as those of the rural Bantu in the various age groups. Clinical diphtheria was rarely encountered under rural conditions but was commoner in the urban

TABLE 14.—*Schick Reactions of Solomon Islanders*
(Adult Males)

	Natives of			Total
	Guadalcanal	Malaita	Florida	
Number tested.....	52	122	22	196
Number with positive reactions.....	2	9	0	11
Number with no reactions.....	50	113	22	185
Percentage with positive reactions.....	4	7.3	0	5.6

natives, and 53 per cent of the patients were in the age group of up to 5 years. The carrier rate for toxigenic *C. diphtheriae* was 3.2 per cent in the rural children and 1.8 per cent in the urban children, with toxigenic:nontoxigenic ratios of 1:1.1 and 1:2.5, respectively. It is interesting to note that approximately 4 per cent of the natives of India have been found to carry *C. diphtheriae*, and a similar carrier rate was found in the native children of Singapore (Hunter³⁰). Murray did not consider that the cutaneous lesions which occur among the Bantu might be diphtheritic, and data were not presented concerning the Schick reactions in children less than 3 years of age.

During our military assignments the opportunity was given to investigate this paradox of high immunity so early in life, associated with relatively little obvious clinical diphtheria, and in particular to determine what role the skin might play. In an early experience, adult native Solomon Islanders were only rarely found to react to a

28. Grasset, E.: Studies on the Nature of Antidiphtheritic Immunity Among South African Bantu by Means of Schick Test and Antitoxin Titrations, *South African M. J.* 7:779-785, 1933; cited by Dudley.²²

29. Murray, J. F.: Diphtheria Amongst the Bantu, *J. Hyg.* 43:159-169, 1943.

30. Hunter, P. S.: Annual Report for 1930, Health Department of Singapore, 1931; cited by Dudley.²²

Schick test (table 14). Likewise in the New Hebrides, Tonkinese children over the age of 3 years were found usually to be negative to the Schick test (table 15). These children all lived in intimate personal contact with one another in a communal nursery under appalling conditions of dirt and were part of the same epidemiologic group as the Melanesian children living on the same plantation. Similar studies were later performed in the Marianas on Chamorros (table 16). Only between the ages of 7 months and 3 years was there any considerable proportion of persons with positive Schick reactions among the

TABLE 15.—*Schick Reactions of Tonkinese Children*
(*New Hebrides*)

	Natives of Given Age				Total
	Up to 6 Mo.	7 Mo. to 1 Yr., Inclusive	13 Mo. to 3 Yr., Inclusive	More than 3 Yr.	
Number tested.....	3	10	28	12	53
Number with positive reactions.....	0	5	3	0	8
Number with no reactions.....	3	5	25	12	45

TABLE 16.—*Schick Reactions of Chamorro Children*
(*Marianas*)

	Natives of Given Age				Total
	Up to 6 Mo.	7 Mo. to 1 Yr., Inclusive	13 Mo. to 3 Yr., Inclusive	More than 3 Yr.	
Number tested.....	7	13	23	45	88
Number with positive reactions.....	0	9	15	2	26
Number with no reactions.....	7	4	8	43	62

Tonkinese and Chamorro children (67 per cent in the case of the latter). Persons more than 3 years of age with positive Schick reactions were rare.

It seemed logical to seek other than the racial factors considered by some²⁹ as an explanation of this phenomenon. The racial element seemed unlikely, since members of diverse races, e. g., Solomon Islanders, Bantu Africans, Tonkinese and Chamorros, exhibited the same phenomenon and since if young enough children were investigated a sharp peak in the curve of positive reactions became apparent. On the other hand, these native people have in common a tropical environment, intimate personal contact and the unwashed state, all of which favor the existence of cutaneous diphtheria. The factor operative early in life to reverse the loss of transplacentally acquired immunity so rapidly was therefore sought in the skin.

The existence of a large cutaneous reservoir of diphtheria became apparent when the skins of the children were examined. Two of 4

Melanesian natives with deep, punched-out ulcers (fig. 17), one of them apparently superinfected yaws, yielded nontoxigenic *C. diphtheriae*. Incidentally, one foul-smelling phagedenic lesion in an adult black New Hebridean was found to contain spirochetes and fusiform bacilli as described by James.² Six of the 53 Tonkinese children had multiple punched-out ulcerative lesions of the skin which resembled the tropical ulcers observed in our soldiers but which were generally more superficial (fig. 18). Four of these yielded organisms with the morphologic and fermentative characteristics of *C. diphtheriae* mitis but which were not toxigenic. Lesions of identical appearance were found in large numbers among the Chamorro children. Fifteen strains of *C. diphtheriae*

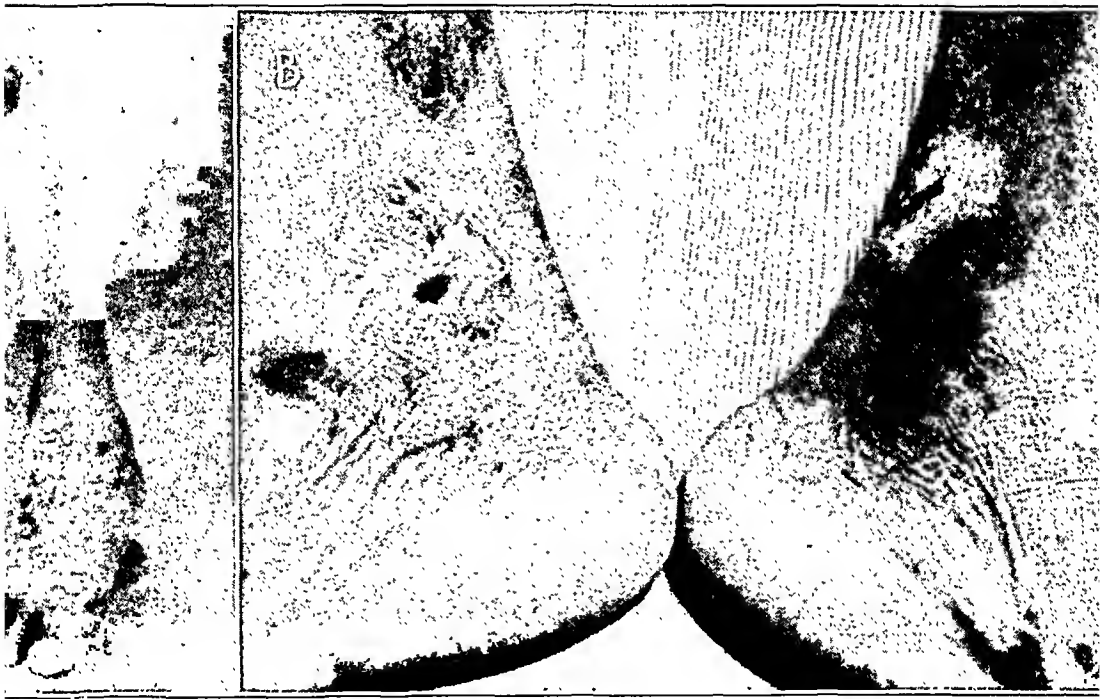


Fig. 17.—*A* (patient TN32), yaws of the right foot with punched-out ulcerations observed in a Melanesian child of the New Hebrides. A typical "ecthymatous" ulcer of the skin is also shown. The ulcerative lesions in both instances contained nontoxigenic *C. diphtheriae*.

B (patient TN4), chronic ulcers of ankles containing *C. diphtheriae* (nontoxigenic) observed in a Melanesian native of Espiritu Santo.

mitis were tested for toxigenicity, and one of these was found to be toxigenic. It is interesting to note and not easy to explain that some of these open lesions occurred in older children who showed no reaction to the Schick test. They were most numerous in areas where trauma was most likely to occur, as about the knees, but they also occurred elsewhere. Their appearance at various stages is shown in figure 18. These scars were absent in children less than 7 months of age and were almost universal in those above the age of 3 years. They were

much less numerous among the persons with positive Schick reactions. Studies of 14 Melanesian natives and 12 Tonkinese revealed that they were not nose and throat carriers. In the Marianas, however, 2 of 18 natives were found to harbor *C. diphtheriae* in the nasopharynx.

All these observations indicate that an enormous reservoir of *C. diphtheriae* exists in tropical and hot desert regions, probably throughout the world, and that the damp skin in closely associated and unwashed



Fig. 18 (patient TN38).—Multiple ulcers in a Tonkinese child, aged approximately 2 years. Some have a punched-out appearance. Some are partly or completely scarred, with bronze-violaceous pigmentation of the surrounding skin. Atoxic *C. diphtheriae* was observed in a culture of material from one of the ulcers.

herds may be the source as well as the immunizing agency. The barrier of cleanliness accounts for the fact that white people living in the tropics are always more susceptible than the natives, as indicated by the results of the Schick test, and that the former often have clinical nasopharyngeal diphtheria, sometimes in epidemics. One such epidemic

was observed by Fox and MacDonald (cited by Forbes³¹) in a school at Shillong in Assam, India, that very region where tropical ulcers have been so common in the natives as well as among the Allied Forces.

In a tropical country such as Formosa, where there is a reservoir group analogous in environment to that of the Tonkinese in the New Hebrides, as well as a relatively well-to-do and clean group, nasopharyngeal diphtheria may become the commonest disease of bacterial causation.³²

Among troops under conditions of combat in the tropics the situation becomes entirely analogous to that of the natives in their usual state. First, the skin is both warm and moist so that nasopharyngeal flora find conditions in the integument similar to those in the pharynx. Even in temperate zones nurses and others in contact with diphtheritic patients have been found to harbor this organism in the skin, e. g., under the finger nails. There is, moreover, often intimate contact with others in foxholes which often are of a three man or communal type. Under some circumstances, as in the Marianas, there was also frequent contact with the native population. Furthermore, during combat numerous minor traumas occur. The important difference between the native and military groups is that in the adult soldiers there is a much higher proportion of persons susceptible to diphtheria. Thus, *C. diphtheriae*, once established, spreads readily not only from skin to skin but also from skin to nasopharynx and in the reverse direction. Direct evidence of the pharyngeal source of an extrapharyngeal infection is the case of diphtheria of the penis illustrated in figure 9A.

The original source of the *C. diphtheriae* is difficult to determine. Carriers are always present in our own military population³³ and the native reservoir may at times be important.

SUMMARY AND CONCLUSION

Tropical ulcers of the deep, punched-out type occurring in soldiers under combat conditions in the South and Central Pacific areas often contain toxigenic *C. diphtheriae*, particularly when cultured within six weeks of onset.

A simple but careful technic is necessary to cultivate the organisms. Blood agar plates of slightly alkaline reaction, prepared so as to avoid

31. Forbes, J. G.: *The Prevention of Diphtheria*, Medical Research Council, Special Report Series, no. 115, London, His Majesty's Stationery Office, 1927.

32. *Epidemiology of Diseases of Naval Importance in Formosa*, United States Navy Department, Bureau of Medicine and Surgery, 1944.

33. Meehan, J. W., and Michie, H. C.: *Diphtheria, in Ireland*, M. W.: *The Medical Department of the United States Army in the World War*, Washington, D. C., Government Printing Office, 1928, vol. 9, chap. 6, p. 233.

hemolysis and streaked in a manner to assure well isolated colonies, are most satisfactory for obtaining rapid and easily recognizable cultures.

The ulcers are disabling in themselves when they occur on the extremities, as they do most commonly.

Neuritis is an occasional complication of apparently purely cutaneous diphtheria, in which case the cranial nerves are rarely, if ever, involved.

Diphtheria should be considered the most probable cause of neuritis, even in persons found to have positive Schick reactions, among troops evacuated from tropical regions, particularly North Africa, India, Burma and the islands of the Pacific.

Evidence gathered from controlled experiments indicates that penicillin locally applied in isotonic solution of sodium chloride to the lesions, with the patient resting in bed, is the treatment of choice at present.

The fact that more persons with positive Schick reactions will be found among any group who have diphtheritic ulcers than among the general population suggests that the state in which no reaction can be elicited by the Schick test is at least to some extent protective against the development of tropical ulcers.

Diphtheria of the skin can result in autoinfection of the nasopharynx in persons with positive Schick reactions, and it also has epidemiologic importance, especially since the cutaneous form has often not been recognized. It may spread from skin to skin, as seems usually to be the case, or from skin to pharynx or the reverse. This was demonstrated in tracing contact infections in a hospital and in observing the course of outbreaks in three military divisions in which cutaneous and nasopharyngeal diphtheria were concomitant. The possibility is suggested, after one reviews recent trends in the incidence of diphtheria, that troops returning immediately from tropical and desert regions may be a hazard to large masses of susceptible civilians.

The existence of a tremendous cutaneous reservoir of diphtheria in natives of the tropics is demonstrated. The presence of *C. diphtheriae* in the skin accounts for the gradual immunizing of these people so early in life.

The factors that conspire to make cutaneous diphtheria relatively so important in the tropics are (1) the warm, moist condition of the skin, (2) the intimate association of the herd and (3) the unwashed state. When susceptible populations, such as white soldiers, are forced by the vicissitudes of combat into the same conditions, then severe faucial as well as the commoner cutaneous forms of diphtheria become widespread.

METHEMOGLOBINEMIA

Treatment with Ascorbic Acid

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CYANOSIS is caused most frequently by cardiac or pulmonary disease, but it may be the result of an increased concentration of methemoglobin, among other etiologic factors. In the absence of cardiac or pulmonary disease further study of the blood to establish or exclude the presence of this hemoglobin derivative is of considerable importance. We have recently encountered 2 patients presenting cyanosis as an important symptom. In 1 the disease is of unusual interest in that a spontaneous formation of methemoglobin was apparently the cause of the cyanosis. A similar syndrome was described by Stokvis in 1902 and named enterogenous cyanosis.¹ Since that time a few additional reports of spontaneously occurring methemoglobinemia in the absence of drug therapy have been described.² Unfortunately, laboratory examinations of the blood pigments were not always made. In the other patient sodium nitrite therapy was the cause of the cyanosis.

Methemoglobinemia is commonly accompanied not only with cyanosis but also with disturbances in gastrointestinal function; frequently diarrhea, usually of long duration, has been noted. In 1 of our patients the combination of cyanosis and gastrointestinal symptoms was prominent. In both patients methemoglobinemia was suspected and confirmed by laboratory studies.

1. Stokvis, B. J.: Casuistic Contributions to the Autotoxic Enterogenous Cyanosis, *Nederl. tijdschr. v. geneesk.* **2**:678, 1902.

2. (a) Talma, S.: Intraglobuläre Methaemoglobinaemie bei den Mensch, translated, *Berl. klin. Wchnschr.* **39**:865, 1902. (b) Berron, G. A.: Enterogenous Cyanosis (Stokvis Syndrome), *Rev. méd. Yucatan* **13**:15, 1924. (c) Innes, F. R.: Case of Enterogenous Cyanosis, *Indian M. Gaz.* **66**:262, 1931. (d) Dunaevskiy, M. I., and Kozlovskaya: A Case of Autotoxic Methemoglobinemia, *Vrach. delo* **22**:367, 1940. (e) Traxler, P. S.: Methemoglobinaemia or Enterogenous Cyanosis, *M. Bull. Vet. Admin.* **20**:227, 1943. (f) King, E. J.; Gilchrist, M., and White, J. C.: A Case of Methemoglobinemia, *Biochem. J.* **38**:8, 1944.

Of particular importance in both cases was the striking response of the cyanosis to treatment with ascorbic acid, with concomitant alleviation of all clinical symptoms. We were not aware that ascorbic acid had been previously used at the time it was employed in the treatment of our first patient; however, perusal of the literature has since revealed that Lian and associates³ were the first to use ascorbic acid in the treatment of methemoglobinemia. Subsequently other reports appeared.⁴ Descriptions of the clinical observations in our patients and of their response to treatment with ascorbic acid follow:

CASE 1.—M. K., a 54 year old obese white woman, was admitted to the surgical service of Dr. William Erb in the Philadelphia General Hospital on July 8, 1944, because of a pain of six hours' duration in the right lower abdominal quadrant. From 1940 to 1943, during which time friends began to notice a change in the color of her skin, the patient had been taking silver nitrate pills for a "stomach ulcer." The patient took a teaspoonful of a saline cathartic a day for five or six months preceding admission, until she began to feel "sick to her stomach." A week before admission transient nonradiating pain in the right upper abdominal quadrant developed, which she stated was treated with mild mercurous chloride by her physician. This pain became generalized on the day before admission, and it was associated with several loose, watery, greenish stools. On the day of admission the patient was vomiting.

Physical examination on admission showed a temperature (oral) of 100 F., pulse rate 100 beats per minute and respiration rate 28 per minute. The patient, who on gross examination was retching and appeared acutely ill, was well developed and well nourished. The skin and mucous membranes showed the characteristic changes of argyria. The blood pressure was 130 systolic and 80 diastolic, but examination of the heart revealed no other abnormalities. The lungs were normal to auscultation and percussion. The abdomen showed poorly localized tenderness throughout but was soft, and peristalsis was normal.

Laboratory Examination.—Laboratory studies showed hemoglobin content 14 Gm. per hundred cubic centimeters and leukocytes 7,800 per cubic millimeter, with a normal differential count. The serum protein level was 6.9 Gm. per hundred cubic centimeters and chlorides as sodium chloride 584 mg. Sugar, urea and carbon dioxide-combining power were normal. The reaction to the Kline test was negative. On July 10 the icterus index was 22, but by July 19 it had fallen to 5. The serum cholesterol level was 272 mg. per hundred cubic centimeters, of which 159 mg. was esterified. Roentgenologic examination of the gallbladder showed poor function, but no stones or gross abnormalities were visible.

On admission a tentative diagnosis of acute cholecystitis was made. The patient was treated with morphine, atropine, 1/100 grain (0.6 mg.) of glyceryl

3. Lian, C.; Frumusan, P., and Sassier: Méthémoglobinémie congénitale et familiale: action favorable de l'acid ascorbique, Bull. et mém. Soc. méd. d. hôp. de Paris 55:1194, 1939.

4. (a) Denny, J.; Murdock, E. T., and Rogan, J. J.: Familial Idiopathic Methemoglobinemia with a Note on the Treatment of Two Cases with Ascorbic Acid, Brit. M. J. 1:721, 1943. (b) Graybiel, A.; Lilienthal, J. L., and Riley, R.: The Report of a Case of Idiopathic Congenital (and Probably Familial) Methemoglobinemia, Bull. Johns Hopkins Hosp. 76:155, 1945. (c) King, Gilchrist and White.^{2f}

trinitrate and fluids intravenously administered. The temperature became normal in six hours, but the patient still complained of pain in the abdomen and continued to vomit. It was noticed that, although the argyria was prominent, the nail beds appeared cyanotic; the diagnosis of enterogenous cyanosis was suggested. On July 10 a specimen of blood was examined spectroscopically and showed the presence of 3.6 Gm. of methemoglobin.⁵ The plasma ascorbic acid level was 0.2 mg. per hundred cubic centimeters. Ascorbic acid therapy was instituted; the patient was given 500 mg. daily by mouth in divided doses for three days. There was noticeable improvement in symptoms within twenty-four hours. By the end of forty-eight hours the patient was able to tolerate food without pain

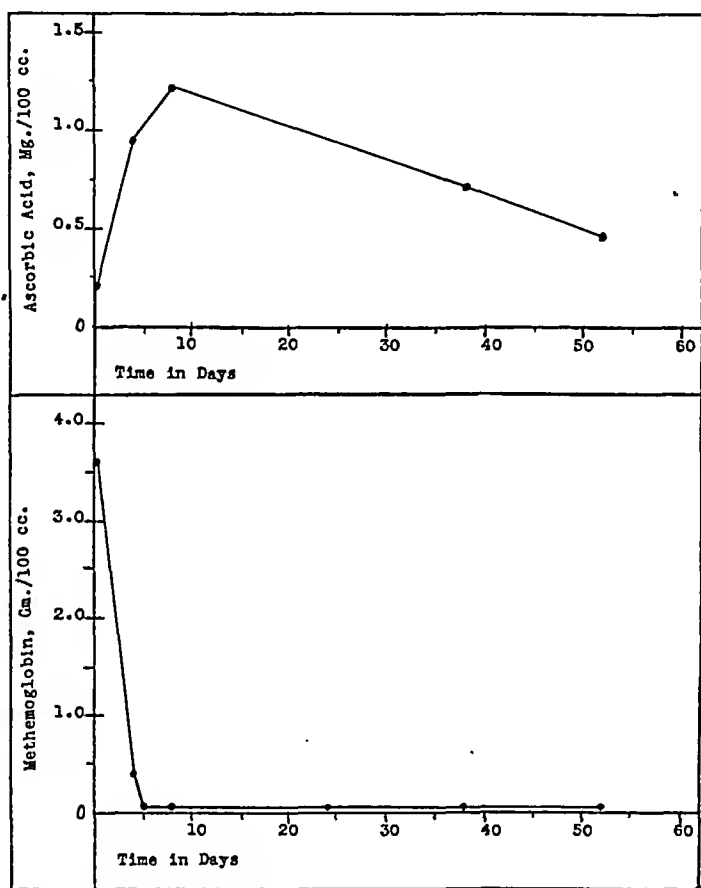


Chart 1 (case 1).—The upper curve portrays the ascorbic acid level of the blood after oral administration of a total of 4,500 mg. in the first six days of treatment. The lower curve illustrates the reduction in the methemoglobin content of the blood concomitant with the administration of ascorbic acid.

or vomiting. In seventy-two hours the methemoglobin level was merely a trace and the ascorbic acid level was 0.95 mg. per hundred cubic centimeters. The patient was then given 1,000 mg. of ascorbic acid daily. On July 15, five days after beginning therapy, there was no methemoglobin demonstrable in the blood. Since

5. Methemoglobin was determined spectroscopically by the procedure of Austin and Drabkin (Austin, J. H., and Drabkin, D. I.: Spectrophotometry of Methemoglobin, *J. Biol. Chem.* **112**:67, 1935) with a Bausch and Lomb visual spectrophotometer.

the patient was symptom free, she was discharged on July 26 and placed on a fat-free diet, with the diagnoses of acute cholecystitis, argyria and methemoglobinemia. Follow-up studies at monthly intervals have shown no return of the methemoglobin nor complaints referable to the gastrointestinal tract. An attempt was made to place the patient on a low ascorbic acid diet to reproduce the syndrome, but the patient was uncooperative.

CASE 2.—A. R., a 69 year old white woman, was admitted to the ophthalmologic ward of the Philadelphia General Hospital, service of Dr. Diechler, because of severe pain and a loss of vision in the right eye of three weeks' duration and a loss of vision in the left eye of thirty-six hours. The patient complained of

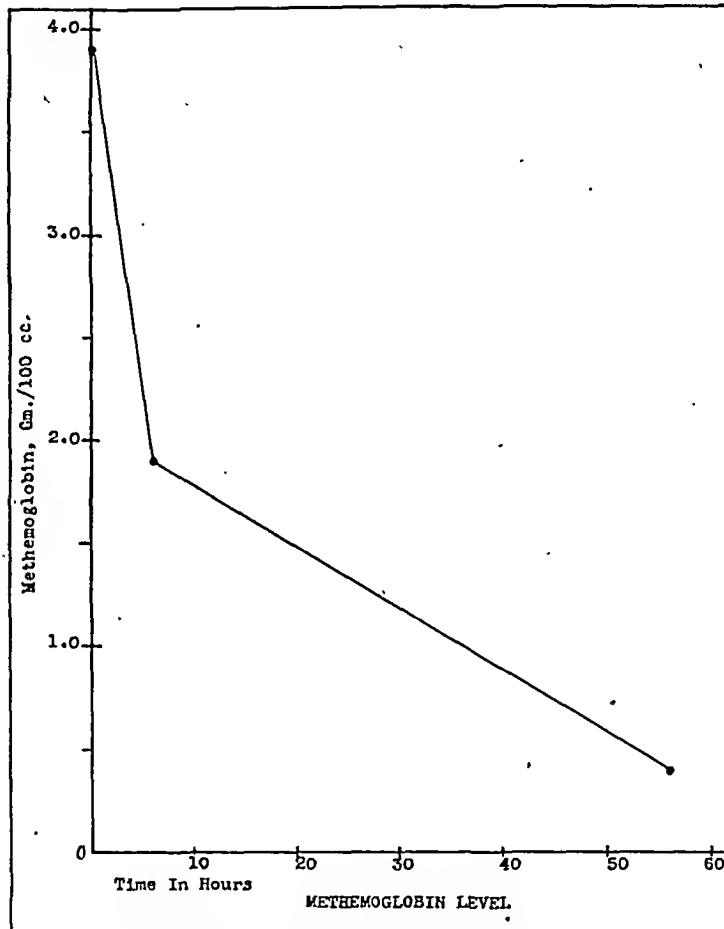


Chart 2 (case 2).—Methemoglobin level of the blood after intravenous administration of a total of 1,000 mg. of ascorbic acid in the first nine hours of treatment. No additional ascorbic acid was administered after the initial nine hour period.

rings around lights, loss of vision and vomiting. There was also a history of mild exertional dyspnea for the past three years. On physical examination the blood pressure was 200 systolic and 100 diastolic. The eyes showed signs of acute congestive glaucoma. Aside from a slight enlargement of the heart the physical examination failed to reveal other significant abnormalities.

On March 23 the patient received 6 cc. of an old solution of sodium nitrite. The exact sodium nitrite content is not known but it was estimated to be between 0.5 to 2.0 Gm. The patient immediately vomited. In one-half hour the patient's blood pressure had fallen to 90 systolic and 50 diastolic. The respirations were

depressed, and slight cyanosis was noted that night. The next morning, March 24, the blood pressure had returned to 180 systolic and 100 diastolic. However, there was an extreme cyanosis of the body, most pronounced in the face and extremities. A sample of blood taken at this time showed 3.9 Gm. of methemoglobin per hundred cubic centimeters when examined spectroscopically. At 12:30 p. m., twenty-four hours after the original medication, 500 mg. of ascorbic acid was given intravenously. Within four hours there was a noticeable decrease in the amount of cyanosis. A further dose of 200 mg. of ascorbic acid was given intravenously. At 6.30 p. m. the cyanosis had disappeared clinically, and the methemoglobin level was 1.9 Gm. A total of 300 mg. was given in two doses intravenously during the remainder of the day. Fifty-six hours after initial therapy the methemoglobin level was 0.4 Gm. per hundred cubic centimeters.

COMMENT

Methemoglobin is the derivative formed by the oxidation of hemoglobin iron to the ferric state, with resultant loss of oxygen combining capacity. By the action of strong reducing agents methemoglobin iron is reduced to the ferrous state and the ability to form oxyhemoglobin restored.

In man, methemoglobinemia may be produced by drugs such as acetanilid and acetophenetidin, by oxidizing agents such as chlorates (used in gargles, matches and explosives), by nitrites, glyceryl-trinitrate and bismuth subnitrate (used in control of diarrhea) and by aniline dyes and their various derivatives. The formation of methemoglobin, in the absence of drug therapy, has been speculatively attributed to absorption of toxic products from the intestinal tract. There is, moreover, increasing evidence that the equilibrium hemoglobin \rightleftharpoons methemoglobin is shifted to the normal state by virtue of the glycolytic systems resident in the erythrocyte.⁶ Any toxic product tending to inactivate or slow this glycolysis would bring about increasing concentrations of methemoglobin.

Cyanosis due to methemoglobinemia becomes clinically evident, according to Goodman and Gilman,⁷ when the methemoglobin attains a level of 3 Gm. per hundred cubic centimeters of blood. Vigness and associates⁸ found that cyanosis resulting from the administration of sulfanilamide became evident with a methemoglobin level of 12.3 per cent of the total blood pigment.

Treatment of methemoglobinemia has been undertaken in the past by the use of intravenously administered methylthionine chloride.

6. Drabkin, D. L.: Hemoglobin, Glucose, Oxygen and Water in the Erythrocyte, *Science* **101**:445, 1945.

7. Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, The Macmillan Company, 1941.

8. Vigness, I.; Watson, C. J., and Spink, W. W.: Relation of Methemoglobin to the Cyanosis Observed After Sulfanilamide Administration, *J. Clin. Investigation* **19**:83, 1940.

According to Goodman and Gilman,⁷ "methylene blue [methylthionine chloride] has two actions on hemoglobin. In high concentrations it converts the ferrous ion of the reduced hemoglobin to the ferric form, and thus methemoglobin is produced. Low concentrations of methylene blue or the chemically related thionine are capable in vivo of hastening the conversion of methemoglobin back to the form which once more can carry oxygen." It may be postulated that the action of methylthionine chloride in the reduction of methemoglobinemia is the result of the stimulation of tissue respiration, as indicated by the experiments of Warburg,⁹ with the reduction of the methemoglobin accomplished by virtue of an increased enzymatic action of the dehydrogenases.

In contrast to methylthionine chloride, ascorbic acid has been shown to reduce methemoglobin in vitro.¹⁰ The reducing properties of ascorbic acid are well known and have been investigated to a considerable extent. Considering the fact that sodium ascorbate has been administered intravenously in large doses without any deleterious effect and that it is a normal metabolite, it was suggested by one of us (B.D.P.) that the powerful reducing properties exhibited in vitro might be successful in vivo.

At present there is no evidence that methemoglobinemia occurs in subclinical ascorbic acid deficiency or frank scurvy. King and associates,^{2f} who studied a patient with chronic methemoglobinemia, were able to demonstrate conclusively that as the ascorbic acid level of the plasma rose there was a concomitant drop in the methemoglobin of 50 per cent in five days with the oral administration of 300 mg. daily of ascorbic acid. The methemoglobin disappeared completely in twenty days under therapy. They then withheld ascorbic acid and were able to demonstrate that as the ascorbic acid fell to low levels the methemoglobin rose to its previous high levels. Denny^{4a} and Graybiel^{4b} were also able to demonstrate a lowering of the methemoglobin level by oral administration of ascorbic acid. We believe that the low ascorbic acid level encountered in the first case is more fortuitous than etiologic. It is to be emphasized that the use of ascorbic acid in the treatment of methemoglobinemia merely takes advantage of its reducing properties. The possibility that increased susceptibility to methemoglobinemia results from low intake of ascorbic acid requires investigation.

In the first patient the cause of the methemoglobinemia is unknown. So small a quantity as 0.7 mg. of glyceryl trinitrate is probably insufficient to cause the oxidation of approximately 30 per cent of the hemo-

9. Warburg, O.; Kubowitz, F., and Christian, W.: Ueber die katalytische Wirkung von Methylenblau in lebenden Zellen, *Biochem. Ztschr.* **227**:245, 1930.

10. Keise, M.: *Biochem. Ztschr.* **316**:264, 1944.

globin. The saline cathartic taken did not have, to our knowledge, any methemoglobinemia-producing substances. Argyria is not known to be associated with methemoglobinemia, nor was methemoglobin found in another patient with argyria. The nitrate ingested with the silver might cause cyanosis, but this medication had been stopped over six months prior to the patient's admission to the hospital: This case is presumed, then, to be a case of idiopathic methemoglobinemia or enterogenous cyanosis.

In the second patient "nitrite syncope" apparently developed from overdosage or from sensitivity to the drug. Although the exact amount of sodium nitrite given is unknown, the rapid development of cyanosis, which became pronounced eight hours later, shows clearly the relation of the drug therapy to the production of methemoglobin. Without doubt the presence of 35 per cent of the hemoglobin in an unusable form gave this woman a functional hypoxia which in the presence of a poor cardiovascular system was of serious consequence. Because of the severe clinical picture the intravenous use of ascorbic acid was preferred to oral therapy. The clinical evidence plus the results of the laboratory studies furnishes conclusive proof that the methemoglobin in the blood was reduced to hemoglobin. We wish to stress that in the second case the reduction was accomplished in a matter of hours rather than days by the intravenous use of ascorbic acid.

SUMMARY

Administration of ascorbic acid was followed by a rapid decrease in the concentration of methemoglobin in the blood of 2 patients showing cyanosis due to methemoglobinemia. At the same time there was prompt alleviation of other symptoms due to the methemoglobin. Ascorbic acid is far more desirable for this purpose than is methylthionine chloride, which may further increase the concentration of methemoglobin in the blood.

LÖFFLER'S SYNDROME ASSOCIATED WITH CREEPING ERUPTION (CUTANEOUS HELMINTHIASIS)

Report of Twenty-Six Cases

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AND

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WE RECENTLY reported 9 cases¹ of transitory, migratory pulmonary infiltration with peripheral eosinophilia and paucity or absence of systemic manifestations, fulfilling the criteria of Löffler's syndrome. In these cases the syndrome complicated creeping eruption, which was offered as a previously unreported cause of pulmonary infiltration. The purpose of the present report is to record 17 additional cases of pulmonary infiltration complicating creeping eruption, making a total of 26 cases of Löffler's syndrome occurring among 76 cases of creeping eruption.

A report of this larger series is warranted for the following reasons:

- (1) to establish creeping eruption as an additional etiologic factor in the production of the so-called Löffler's syndrome;
- (2) to prove that creeping eruption is not always a localized cutaneous disease;
- (3) to forge an additional link in the chain of circumstantial evidence that the pathogenesis of Löffler's syndrome is an allergic phenomenon.

CREEPING ERUPTION

Creeping eruption (cutaneous helminthiasis), which is endemic in the southeastern coastal regions of the United States, has been considered a purely cutaneous disease.² It is characterized by serpigi-

1. Wright, D. O., and Gold, E. M.: Loeffler's Syndrome Associated with Creeping Eruption (Cutaneous Helminthiasis), *J. A. M. A.* **128**:1082-1083 (Aug. 11) 1945.

2. (a) Cecil, R. L.: *A Textbook of Medicine*, ed. 6, Philadelphia, W. B. Saunders Company, 1943. (b) Sutton, R. L., and Sutton, R. L., Jr.: *Diseases of the Skin*, ed. 10, St. Louis, C. V. Mosby Company, 1939. (c) Yater, W. M.: *The Fundamentals of Internal Medicine*, ed. 3, New York, D. Appleton-Century Company, Inc., 1942. (d) Craig, C. F., and Faust, E. C.: *Clinical Parasitology*, ed. 2, Philadelphia, Lea & Febiger, 1940. (e) Hume, E. E.: *Creeping Eruption* in Tice, F.: *Practice of Medicine*, Hagerstown, Md., W. F. Prior Company, Inc., 1940, vol. 3, p. 695.

nous elevated reddish tunnels or burrows, usually occurring on the exposed surfaces of the skin (fig 1). Kirby-Smith³ first suggested the nematodal origin of these lesions. Kirby-Smith, Dove and White⁴ proved that the filariform larvae of *Ancylostoma braziliense* (hookworm of dogs and cats) produced these lesions. They firmly established the life cycle of this nematode and the epidemiology of the disease. The dog and the cat are natural hosts for this nematode, and they inoculate the soil with their feces containing the ova of *A. braziliense*. The active filariform larvae from these ova remain viable for long periods in sandy soil that is warm and moist, awaiting an opportunity for contact with the skin of human beings. This opportunity occurs most frequently in the vicinity of swimmers, children, soldiers, plumbers and others whose occupation necessitates contact with the soil. Within a few hours after the larva contacts the skin, a pruritic urticarial-like lesion develops at the site of penetration. In seven to seventy-two hours a serpiginous reddish elevated tunnel appears, which increases in length day after day as the larva migrates in the layers of the skin. Intense itching is the rule, and mild cellulitis about the lesion, due to secondary infection, is not uncommon.

Lesions on the feet are frequent and are often misdiagnosed as epidermophytosis and treated with salicylic acid, the effect of this adding to the acute inflammation and masking the classic appearance of the lesion.

Experimental proof of the production of creeping eruption by *A. braziliense* has been offered by Shelmire⁵ and Dove.⁶ Shelmire applied pure cultures of such larvae to the unbroken skin of human beings, and the penetrations of the larvae produced typical lesions of creeping eruption. White and Dove also produced the classic linear serpiginous burrows of creeping eruption by applying cultures of the larvae of *A. braziliense* to human skin, but the application of the larvae of *Ancylostoma canium* produced a papular lesion without the linear burrows. We believe that the creeping eruptions in all our cases were

3. Kirby-Smith, J. L.: Creeping Eruption, *J. Florida M. A.* **4**:95-100 (Oct.) 1917.

4. (a) Kirby-Smith, J. L.; Dove, W. E., and White, G. F.: Creeping Eruption, *Arch. Dermat. & Syph.* **13**:137-175 (Feb.) 1926; (b) Some Observations on Creeping Eruption, *Am. J. Trop. Med.* **9**:179-193 (May) 1929. (c) White, G. F., and Dove, W. E.: The Causation of Creeping Eruption, *J. A. M. A.* **90**: 1701-1704 (May 26) 1928.

5. Shelmire, B.: Experimental Creeping Eruption from a Dog and Cat Hookworm (*A. Braziliense*), *J. A. M. A.* **91**:938-943 (Sept. 29) 1928.

6. Dove, W. E.: Further Studies on *Ancylostoma Braziliense* and the Etiology of Creeping Eruption, *Am. J. Hyg.* **15**:664-711 (May) 1932.

caused by *A. braziliense* because typical linear burrows were present in each of the cases (fig. 1).

Shelmire also showed that repeated cultures of the stool from his 7 spontaneously infected and his 16 experimentally infected patients failed to show intestinal infection from *A. braziliense*. Similarly in our series, repeated examinations of the stool have failed to disclose the presence of the ova or the parasite in the stool. This bears out the general consensus in the literature.

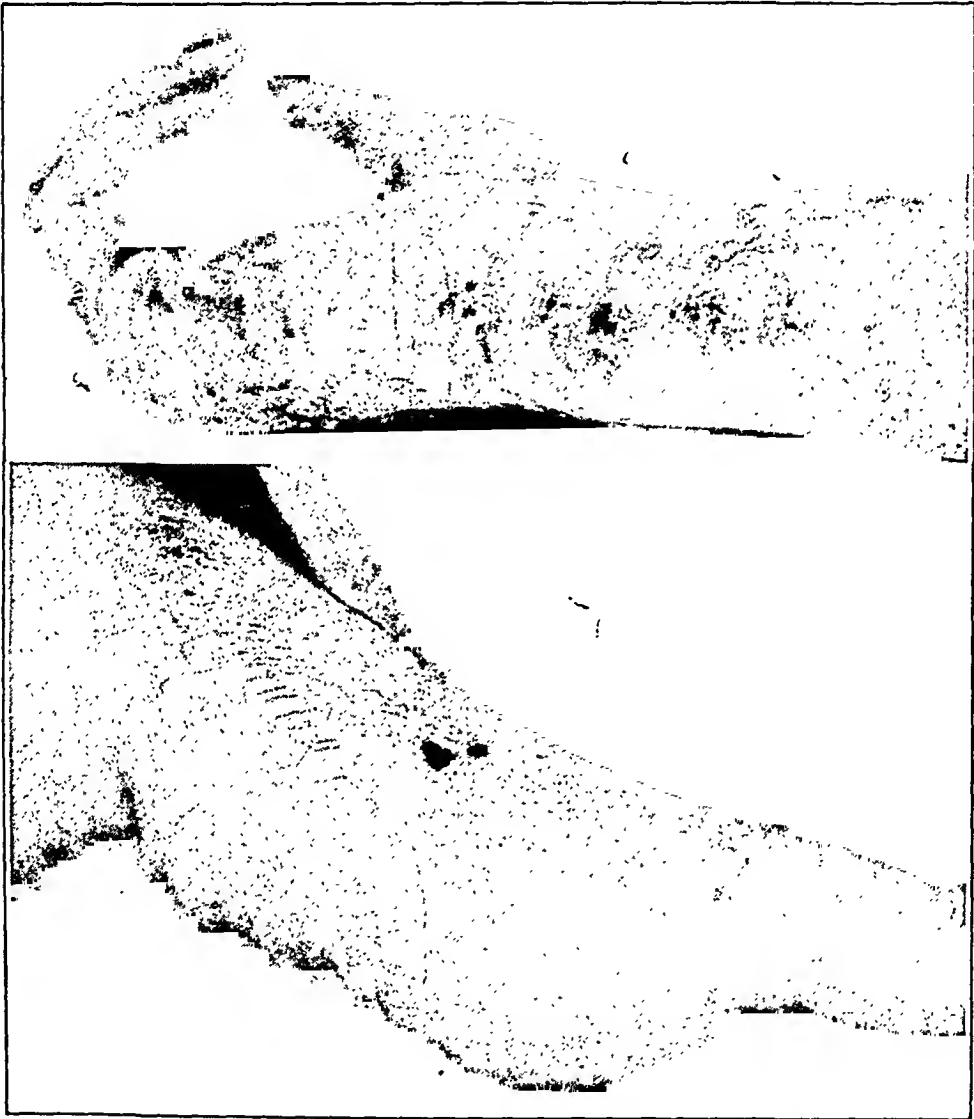


Fig. 1.—The clinical appearance of the classic serpiginous vesicular burrows.

LOEFFLER'S SYNDROME

Since Löffler's⁷ original description of the syndrome of transitory pulmonary infiltration associated with peripheral eosinophilia and

7. Löffler, W.: Zur Differential-Diagnose der Lungeninfiltrierungen; über flüchtige Succedan-Infiltrate (mit Eosinophilie), Beitr. z. Klin. d. Tuberk. **79**: 368-382, 1932.

paucity or absence of systemic manifestations, a voluminous literature has developed. The most striking observation from a perusal of this literature is the multitude of etiologic agents. Löffler⁸ expressed the opinion that this condition represented a tuberculous process on a pathergic basis. In 1935, Engel⁹ ascribed its production to the inhalation of pollen from the privet shrub. Meyer¹⁰ expressed the belief that the inhalation of pollen of the *Convallaria* in Europe was the etiologic factor. Recently, Harkavy¹¹ and Hansen-Pruss and Goodman¹² reported on Löffler's pneumonia complicating chronic asthmatic states. Other etiologic factors that have been reported are: *Ascaris*,¹³ *Trichuris trichiura*,¹⁴ *Strongyloides*,¹⁵ *Taenia saginata*,¹⁶ *Fasciola hepatica*,¹⁷ *Endamoeba histolytica*,¹⁸ trichinas,¹⁹ brucellas²⁰ and

8. Löffler, W.: Die flüchtigen Lungeninfiltrate mit Eosinophilie, Schweiz. med. Wchnschr. **66**:1069-1078 (Nov. 7) 1936.

9. Engel, D.: (a) Ueber eine eigenartige anaphylaktische Erkrankung der Lunge, Beitr. z. Klin. d. Tuberk. **87**:239-250, 1935; (b) Zur Frage des anaphylaktischen Frühjarsödems der Lunge: Bemerkungen zu einer Arbeit von W. Löffler, *ibid.* **89**:323-326, 1937.

10. Meyer, H. E.: Zur Kenntnis flüchtiger mit Eosinophilie im Blut einhergehender Lungeninfiltrate, Med. Welt **11**:1808-1810 (Dec. 25) 1937.

11. Harkavy, J.: Vascular Allergy: III., J. Allergy **14**:507-537 (Nov.) 1943.

12. Hansen-Pruss, O. C., and Goodman, E. G.: Allergic Pulmonary Consolidations, Ann. Allergy **2**:85-108 (March-April) 1944.

13. (a) Baumann, H.: Eosinophilic Pleurisy with Transitory Eosinophilic Pulmonary Consolidation, Schweiz. med. Wchnschr. **74**:326 (April 1) 1944; abstracted, Trop. Dis. Bull. **49**:859-860 (Oct.) 1944.

14. Miller, H.: Transitory Lung Infiltrations Accompanied by Eosinophilia, New England J. Med. **232**:7-10 (Jan. 4) 1945.

15. Berk, J. E.: Transitory Pulmonary Infiltrations, Correspondence, J. A. M. A. **127**:354-355 (Feb. 10) 1945.

16. Benda, R., and Weinberg, L.: Two Cases of Loeffler's Syndrome, Bull. et mém. Soc. méd. d. hôp. de Paris **56**:24-27 (Feb. 14) 1940.

17. Lavier, G.; Bariety, M., and Caroli, J.: Distomatose hépatique et syndrome de Loeffler, Paris méd. **1**:434-439, 1939.

18. Hoff, A., and Hicks, H. M.: Transient Pulmonary Infiltration: A Case with Eosinophilia (Loeffler's Syndrome) Associated with Amebiasis, Am. Rev. Tuberc. **45**:194-199 (Feb.) 1942.

19. Slowey, J. F.: A Case of Transient Pulmonary Infiltration (Loeffler's Syndrome) Associated with Trichiniasis, Ann. Int. Med. **21**:130-135 (July) 1944.

20. Elsom, K. A., and Ingelfinger, F. J.: Eosinophilia and Pneumonitis in Chronic Brucellosis: A Report of Two Cases, Ann. Int. Med. **16**:995-1002 (May) 1942.

azosulfamide.²¹ Because of our observations we add cutaneous helminths as an additional cause. This diversified list of etiologic factors lends credence to the view that Löffler's syndrome is an allergic phenomenon.

CLINICAL DATA

During the summers of 1943 and 1944 we observed 76 cases of creeping eruption with classic cutaneous lesions. It was possible to study 52 of these cases for fourteen days or longer. During this period of study in 26 of the 52 cases there developed transitory, migratory pulmonary infiltration and peripheral eosinophilia, with almost complete absence of clinical signs or symptoms of systemic disease.

TABLE 1.—*Summary of Data from Investigative Procedures*

	Symptoms (76 Cases)	
	No. of Cases	Per Cent of Series
Itching.....	65	85.5
Cough.....	9	11.8
Infection *.....	8	10.5
	Laboratory Data (76 Cases)	
	No. of Tests	Results
Eosinophil count (blood).....	507	High, 51% Low, 1%
Eosinophil count (sputum).....	381	High, 90% Low, 0%
Examination of the stool.....	441	All neg. for <i>A. braziliense</i> <i>E. coli</i> 6 <i>E. nana</i> 4 <i>N. americanus</i> 1 <i>G. lamblia</i> 3
Sedimentation rate.....	395	Elevated* in 8 cases
Cutaneous tests.....	57	75.5% positive 24.5% negative

* In these cases there was secondary infection with local cellulitis.

Our investigative procedures in these cases, summarized in table 1, consisted of roentgenographic examination of the chest every third day, determinations of peripheral and sputal eosinophilia, study of the sedimentation rate, examinations of the stool for ova and parasites and intradermal testing with the antigens from *Ascaris lumbricoides* and *Trichinella spiralis*.

21. Ellis, R. V., and McKinlay, C. A.: Allergic Pneumonia, *J. Lab. & Clin. Med.* 26:1427-1432 (June) 1941.

Data on 4 representative cases have been summarized in tables 2, 3, 4 and 5.

TABLE 2.—*Data on Representative Case **

Day of Disease	Date	Eosinophil Count, % (Blood)	Eosinophil Count, % (Sputum)	Site of Infiltration; Roentgenogram of Chest	Sedimentation Rate (60 Minutes)
5	9/26/44	13	10	None	6.0
11	10/ 2/44	32	60	None	1.5
27	10/18/44	48	0	Lower lobe of the right lung	2.5
33	10/24/44	30	0	None	3.0
47	11/ 7/44	13	Q.N.S. †	None	3.0

* Case 55. The patient was admitted to the hospital on the fifth day of the cutaneous disease with burrows generalized over the trunk anteriorly and posteriorly and over the extremities, upper and lower.

† Q.N.S. means quantity of sputum was not sufficient for a count of eosinophils to be made.

TABLE 3.—*Data on Representative Case **

Day of Disease	Date	Eosinophil Count, % (Blood)	Eosinophil Count, % (Sputum)	Site of Infiltration; Roentgenogram of Chest	Sedimentation Rate (60 Minutes)
11	9/29/44	13	25	None	1.0
14	10/ 2/44	19	25	None	1.0
32	10/20/44	2	0	Right costophrenic angle	12.0
36	10/21/44	3	0	Right costophrenic angle	14.0
43	10/31/44	11	0	None	5.5
50	11/ 7/44	6	0	None	3.0

* Case 48. The patient was admitted to the hospital on the eleventh day of the cutaneous disease, with itching burrows over both buttocks.

TABLE 4.—*Data on Representative Case **

Day of Disease	Date	Eosinophil Count, % (Blood)	Eosinophil Count, % (Sputum)	Site of Infiltration; Roentgenogram of Chest	Sedimentation Rate (60 Minutes)
11	7/13/44	4	35	None	...
20	7/22/44	11	0	Lower lobe of the left lung	1.0
26	8/28/44	19	5	Lower lobe of the left lung (—)	1.0
32	8/ 3/44	22	8	None	3.0
	9/ 6/44	10	30	None	0.5

* Case 25. The patient was admitted to the hospital on the eleventh day of the creeping eruption over the left side of the back and the posterior surfaces of the upper parts of both arms. The patient complained only of itching. On admission to the hospital the patient had a diagnosis of herpes.

TABLE 5.—*Data on Representative Case **

Day of Disease	Date	Eosinophil Count, % (Blood)	Eosinophil Count, % (Sputum)	Site of Infiltration; Roentgenogram of Chest	Sedimentation Rate (60 Minutes)
11	10/11/44	23	0	1.5
20	10/20/44	28	0	Upper lobe of the left lung	5.0
24	10/24/44	..	0	Upper lobe of the left lung	...
32	11/ 1/44	21	0	None	12.0
42	11/11/44	19	0	None	11.0
60	11/29/44	15	0	None	5.0

* Case 47. The patient was admitted to the hospital on the eleventh day of the cutaneous disease, with itching burrows over the right arm and forearm.

Clinical Course.—All patients were afebrile except 8 in whom cellulitis developed, due to secondary infection of the cutaneous lesions. Physical findings were minimal or absent. Slightly decreased resonance, roughened breath sounds and an insignificantly increased respiratory rate, when present, were the only positive thoracic findings. Rales were not heard at any time. Sputum was scant or absent. Except for the local cutaneous irritation and a mild cough that occurred in 9 cases, the patients were not aware of any illness.

Eosinophilia.—Differential blood smears, examined every third day during the period of observation, revealed an eosinophil count ranging from 1 to 51 per cent. The degree of the eosinophilia approximated the extent of the pulmonary consolidation and tended to persist for four to six weeks after the consolidation

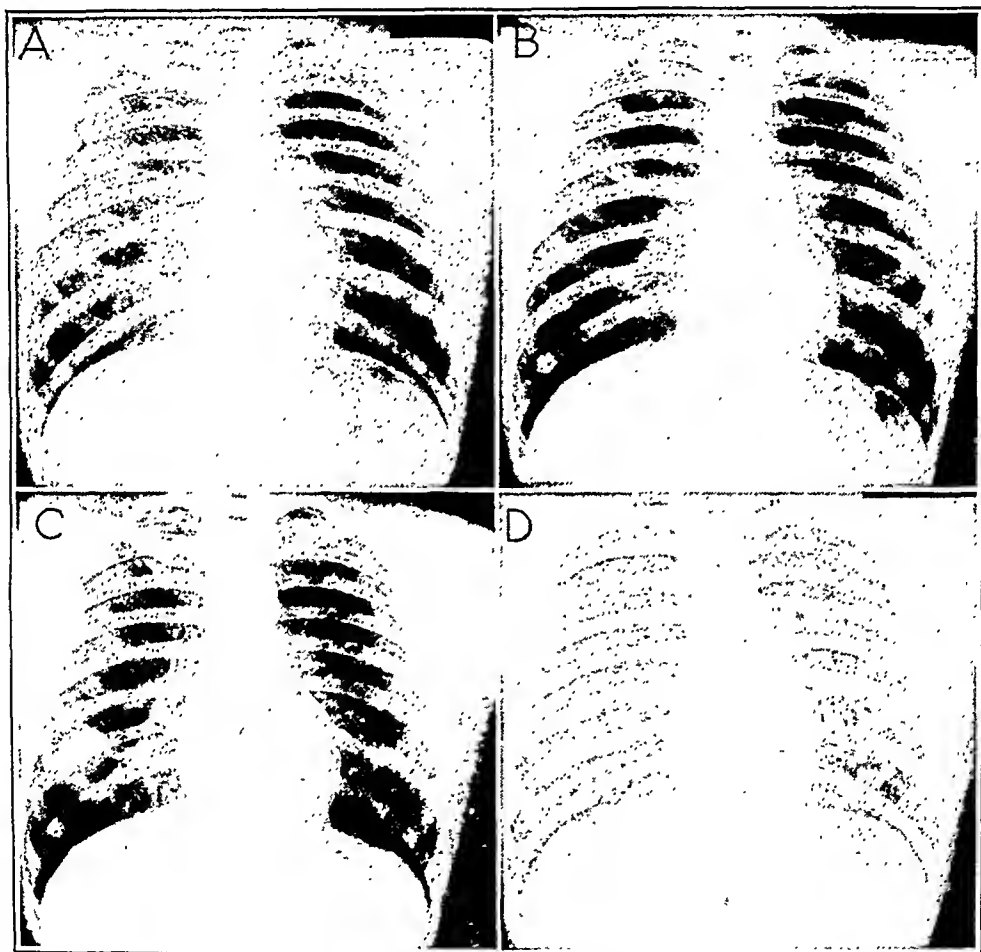


Fig. 2.—The migratory character of the pulmonary lesions in a representative case.

had subsided. This observation is in agreement with those of other investigators.¹² Examinations of the sputum for eosinophils were done every third day, and the count ranged from 0 to 90 per cent. The height of eosinophilia approximated the degree of pulmonary consolidation and also persisted for four to six weeks, despite subsidence of roentgenographic evidence of pulmonary consolidation.

Roentgenologic Studies.—Roentgenographic examination of the chest revealed a patchy infiltration, transient and often migratory in nature, usually not appearing before the seventh day of the cutaneous eruption. When the cutaneous lesions

were untreated, the pulmonary infiltrations continued on a migratory course over a period of weeks. The transient and often migratory character of the lesions is shown by representative roentgenograms of the chest in figure 2. The shadows varied in size from isolated parenchymal lesions, approximately 2 by 3 cm. (fig. 2 A), to patchy involvement of approximately 75 per cent of the pulmonary fields (fig. 3). The supraclavicular fields remained clear in all cases. Cavitation was not seen. Demonstration of transient or migratory infiltration by serial roentgenograms of the chest prevents an erroneous diagnosis of pulmonary tuberculosis or sarcoid.

Examinations of the Stool.—A total of 441 examinations of the stool were performed by Faust's zinc sulfate centrifugal flotation technic. Nematodal ova or parasites were not found except in 1 case in which the patient harbored ova of *Necator americanus*, but in this patient pulmonary infiltration did not develop. Two hundred and four examinations were performed for the 26 patients with

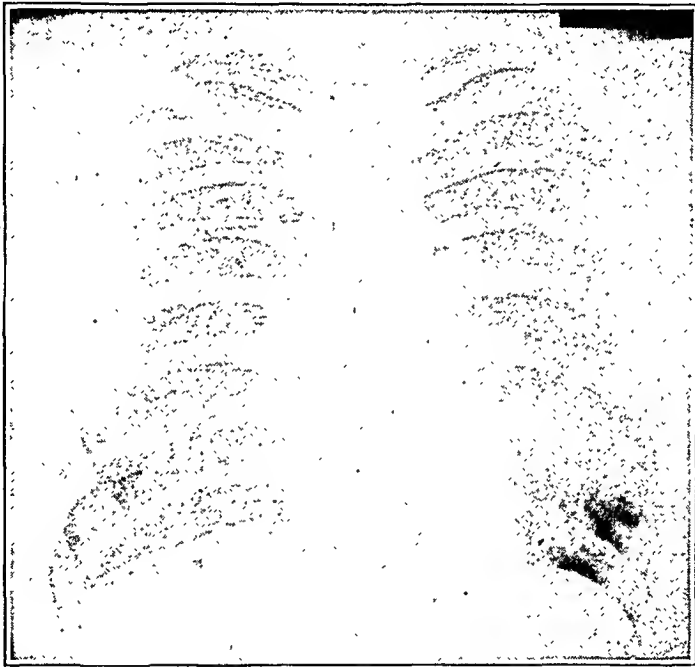


Fig. 3.—The greatest degree of pulmonary involvement seen in the series.

Löffler's pneumonia. Thirteen of them had a total of 172 examinations of the stool over a period of six weeks or more, which is sufficient time to eliminate the possibility of concomitant infestation with the hookworm of human beings. The following intestinal parasites were present in patients with pulmonary infiltration: *Endamoeba coli* and *Endamoeba nana* in 1 patient each and *Giardia lamblia* in 2 patients.

Sedimentation Rate.—The sedimentation rate is of value in differential diagnosis. A total of 395 determinations of sedimentation rate were made by the Wintrobe method. All readings were approximately normal except in 8 cases. In 6 of these the abnormal readings were due to the secondary infection and cellulitis present about the cutaneous lesions, and they returned to normal as the cellulitis cleared, despite the persistence of pulmonary lesions. In the 2 remaining

cases the rapid sedimentation rates coincided with the pulmonary infiltration, but they returned to normal before the infiltration cleared.

Cutaneous Tests.—Brunner indicated that testing with extracts of *A. lumbricoides* and *T. spiralis* was sufficient for the diagnosis of any nematodal infestation. Intradermal tests with aqueous extracts of *Ascaris* and *Trichina* were performed for 57 patients. Seventy-five per cent of these patients showed a positive reaction to one or both of the antigens. This suggests that *A. braziliense*, a member of the roundworm group, had antigenetically sensitized the host and that this may be the causative factor in producing the transitory, migratory pulmonary infiltration. No correlation between the degree of cutaneous sensitivity shown in the test and the extent of pulmonary infiltration was observed.

COMMENT

The pulmonary infiltrations in this series of cases were not caused by concomitant infestation with the hookworms of human beings because:

1. Classic linear burrows were present in all cases.
2. Neither nematodes nor ova were found in 204 stool examinations. Thirteen of the patients with pulmonary lesions had repeated examinations (a total of 172) for a period of more than six weeks.
3. No nematodal larvae of any type were found in 381 examinations of sputum.

Our failure to identify the ova or the parasites of *A. braziliense* in 441 examinations of the stools confirms the reports of others ²² that in human beings intestinal infestation with ancylostomes of this species is almost unknown. However, it should be pointed out that Bonne ²³ observed *Ancylostoma* invading the wall of the human intestine in a total of 10 cases. In only 1 case was the invading nematode *A. braziliense*. He suggested that perhaps the reason for the inability to find the larvae of *A. braziliense* in the stool was due to the fact that these larvae have the habit of burrowing either subepidermally in the skin or submucosally in the intestinal tract.

These observations lead to three possibilities concerning the pathogenesis of the pulmonary infiltrations associated with creeping eruption.

1. In view of Boone's reports, the pulmonary infiltrations could be caused by transpulmonary larval migration, just as with *Necator americanus* or *Ancylostoma duodenale*.
2. If we ignore Boone's reports and adhere to our observations and the reports of others of failure to find *A. braziliense* in the

22. Footnote 4. Shelmire.⁵ Dove.⁶

23. Bonne, C.: (a) Invasion of the Submucosa of the Human Small Intestine by *Ancylostoma Braziliense*, *Am. J. Trop. Med.* **17**:587-594 (July) 1937; (b) Invasion of Wall of Human Intestine by *Ancylostomes*, *ibid.* **22**:507-509 (Sept.) 1942.

stools of patients with creeping eruptions, the pulmonary lesions could be caused by the larvae reaching the lung and dying there, thus failing to reach the intestinal tract.

3. *A. braziliense* remaining subepidermal elaborates an exotoxin which antigenically sensitizes the host, as suggested by the intradermal reactions to test antigens of *Ascaris* and/or *Trichina*, and the lung as shock tissue reacts to the blood-borne antigens from the larvae in the cutaneous lesions.

Regardless of which mechanism proves to be correct, the pulmonary infiltrations are caused by an antigenic response to the presence of either the larvae or its blood-borne exotoxin.

CLINICAL SIGNIFICANCE AND DIFFERENTIAL DIAGNOSIS

Since there is little objective and no subjective evidence of pulmonary or systemic disease, the chief clinical significance is in the differential diagnosis. If the clinician is not aware of the possibility of pulmonary infiltration complicating creeping eruption, an erroneous diagnosis of virus pneumonia, pulmonary tuberculosis or sarcoid may be made. The results of the treatment of the cutaneous lesions, serial roentgenograms of the chest and normal sedimentation rates will differentiate these conditions.

TREATMENT

Treatment of the cutaneous lesions consists of the application of ethyl chloride, which is sprayed for thirty seconds daily over an area 4 to 5 cm. in diameter about the ends of the tunnels. If the cutaneous lesions remain untreated, the larvae continue their migration in the skin for several weeks, and the transient, migratory pulmonary infiltrations may continue. In 1 untreated patient pulmonary lesions developed fifty-nine days after the appearance of cutaneous lesions, and the infiltration persisted for thirty days. Roentgenographic evidence of pulmonary infiltration promptly subsides when the cutaneous lesions are properly treated.

SUMMARY

Pulmonary lesions compatible with the diagnosis of Löffler's pneumonia occurred in 26 of 52 cases of creeping eruption. The lesions were observed by means of serial roentgenograms of the chest for fourteen days or more.

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TREATMENT OF GUMMATOUS HEPATIC SYPHILIS WITH PENICILLIN

Report of Two Cases *

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THIS is the first report dealing with penicillin as used in the treatment of gummatous hepatic syphilis. Two cases are presented.

REPORT OF CASES

CASE 1.—A 49 year old Negro housewife was admitted to the hospital on Oct. 25, 1943, because of right-sided abdominal and thoracic discomfort of four years' duration and soreness of the right knee of two years' duration. The past and family histories were not pertinent except that a blood serologic test for syphilis had been negative in 1929. The patient said that she had contracted no venereal diseases.

For four years she had had attacks of "pleurisy" on the right side, which had at times required medical care. One and a half years before admission she began to be troubled with pain and "tightness" in the right upper quadrant of the abdomen, together with a feeling of fulness in the region of the liver. About every two months she had attacks with colic-like discomfort in this area which lasted a day or so and which were associated with constipation but never with nausea, vomiting, jaundice, light-colored stools or dark urine. About two years prior to entering the hospital she had fallen and hurt her right knee; it had become swollen, hot and tender. This condition had gradually become worse until, at the time of admission, she limped noticeably and had "shooting pains" in the involved parts. The left knee, without trauma, had become similarly affected, although to a lesser degree. During the preceding year she had lost about 16.3 Kg. (36 pounds) in weight and had become so generally debilitated that hospitalization was thought necessary.

Physical examination revealed an emaciated, chronically ill Negro woman. Her appearance is shown in figure 1A. The blood pressure was 112 mm. of mercury systolic and 64 mm. diastolic. A loud blowing systolic murmur was heard over the entire precordium, and the aortic second sound was accentuated. The lungs seemed normal. The abdomen was remarkable, the liver being enlarged to between 11 and 12 cm. below the right costal margin in the midclavicular line. It was tender, and its anterior surface presented several large nodules. No bruit could be heard over this mass. About 4 cm. below the costal margin, the spleen

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The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Johns Hopkins University.

was also felt. There was no evidence of ascites, dilated superficial veins or hemorrhoids. The right knee joint was somewhat swollen and tender; the patella was floating, and there was excess fluid in the synovial cavity. The patella was irregular in contour and was exquisitely sensitive when compressed, although it could be painlessly moved about. There was also moderate tenderness over the lower third of the femur and the upper third of the tibia. Similar conditions of lesser severity were present in the left knee. The neurologic examination revealed no abnormalities except generalized hyperreflexia.

Laboratory tests yielded the following data: The Eagle serologic test for syphilis was positive; the flocculation titer was 128 units. A complement fixation test and the Frei test for lymphogranuloma venereum were negative, as was the routine Ito-Reenstierna test for chancroid. There was microcytic anemia, with 4,210,000 erythrocytes per cubic millimeter of blood, as well as achromia, anisocytosis and poikilocytosis. There was 7.0 Gm. of hemoglobin per hundred cubic centimeters of blood. The leukocyte count was not abnormal, and the icteric index was 5.0

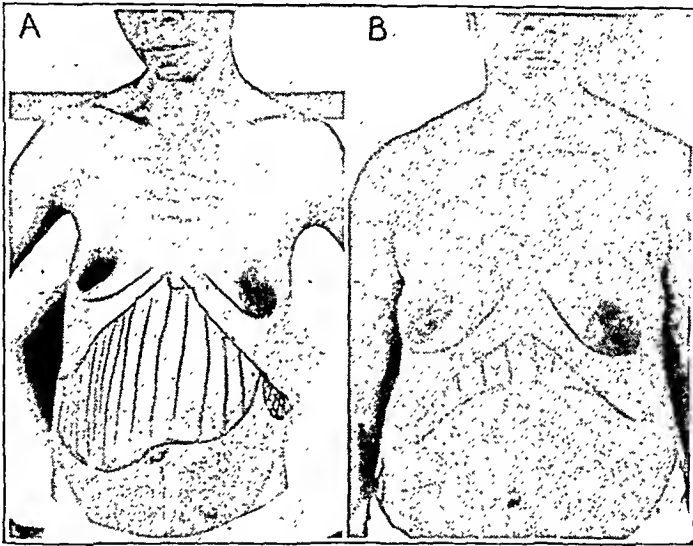


Fig. 1 (case 1).—Response of benign late syphilis (gummas) of the liver to penicillin therapy: *A*, before treatment; *B*, six hundred and eighty-six days after initiation of therapy.

units. A urinalysis done on the patient's admission to the hospital showed 3 plus urobilin but no bilirubin; the results of subsequent tests were within normal limits. The results of chemical analyses of the blood were reported as follows: total serum protein, 8.19 Gm. per hundred cubic centimeters; albumin-globulin ratio, 0.72; cholesterol, 200 mg. per hundred cubic centimeters of blood. The serum phosphatase activity was 16.5 Bodansky units per hundred cubic centimeters of serum. The prothrombin time was normal, as were the results of the hippuric acid and sulfobromophthalein sodium tests of hepatic function. A cephalin flocculation determination was strongly positive. In the congo red test for amyloidosis 91 per cent of the dye was excreted in one hour (a normal result). Subsequent variations in significant laboratory and clinical data are presented in figure 2.

Roentgenograms demonstrated areas of radiolucency in the patellas and proliferative activity around the middle thirds of both femurs. These were characterized by both destruction and proliferation of bone and were interpreted as syphilitic in origin (fig. 3*A*).

The huge, nodular, sensitive liver, the associated syphilitic osteoperiostitis, the positive blood serologic test and a temperature which ranged as high as 103.2 F. (rectal) were considered to be evidence justifying the diagnosis of multiple hepatic gummas. The splenomegaly was not inconsistent with this diagnosis. The long duration of symptoms with the comparatively minor impairment of general health was regarded as a decisive factor in the diagnosis. The use of penicillin was undertaken partly as a therapeutic test, with the expectation that the tenderness and the fever would disappear rapidly but that a rapid diminution in the size of the liver was not to be expected.

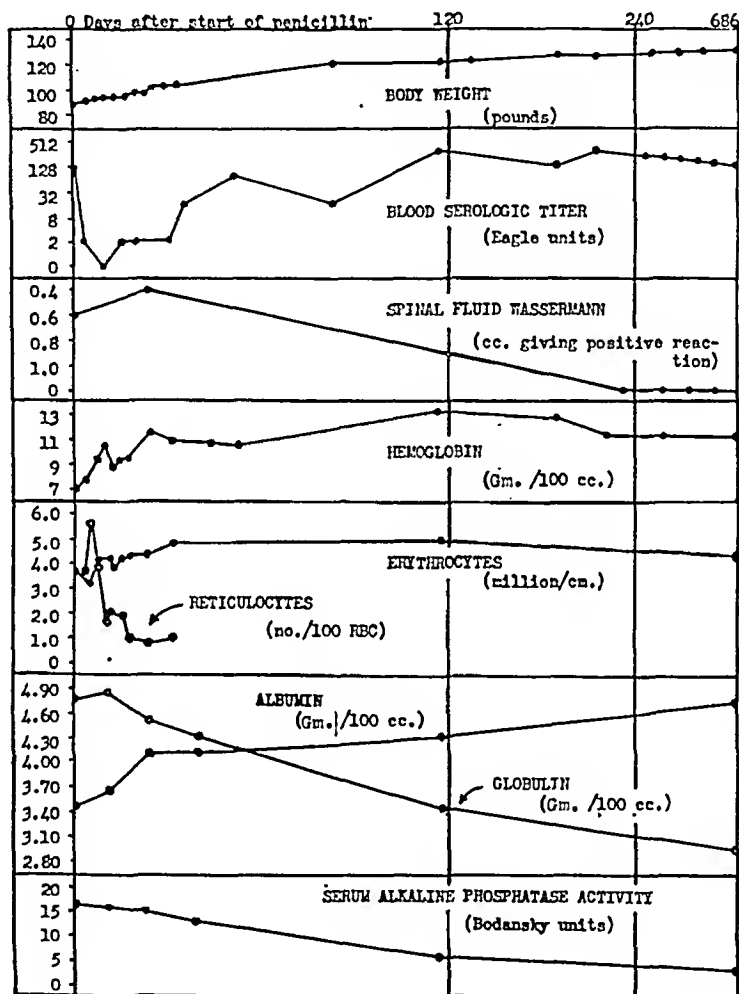


Fig. 2 (case 1).—Improvement following penicillin therapy.

On Oct. 29, 1943, the administration of sodium penicillin in isotonic solution of sodium chloride was begun; the patient received 5,000 Oxford units intramuscularly every three hours for sixty-four injections in eight days, a total of 320,000 units. This dose was arbitrarily selected on an experimental basis only. On October 31 the temperature became normal and remained normal (fig. 4). The tenderness previously associated with the enlarged liver and the knees had dramatically diminished. No changes, however, could be noted in the size of the liver or the spleen. A pronounced reticulocyte response occurred, and on November 15 the hemoglobin content had risen to 9.4 Gm. per hundred cubic centimeters of blood. The excess of synovial fluid was now gone from the joint cavity of the right knee.

By November 24, twenty-seven days after the start of penicillin therapy, the spleen could no longer be felt.

Because of the excellent initial response to this antibiotic substance, the low total dose originally employed and the potential gravity of the patient's illness, a second course of penicillin was thought desirable. On November 26, sodium penicillin therapy was resumed; 10,000 Oxford units were given intramuscularly every three hours for sixty injections in seven and a half days, to a total of 600,000 units. There was no additional clinical improvement during this second course. Altogether, in the two courses, 920,000 units of penicillin was administered.

At the time of discharge from the hospital, on December 8, she had regained 4.5 Kg. (10 pounds) in body weight, and even weight bearing caused no discomfort in her knees. The hemoglobin had risen to 10.6 Gm. per hundred cubic centimeters of blood and the albumin-globulin ratio to 0.96. The size of the liver had not appreciably lessened.

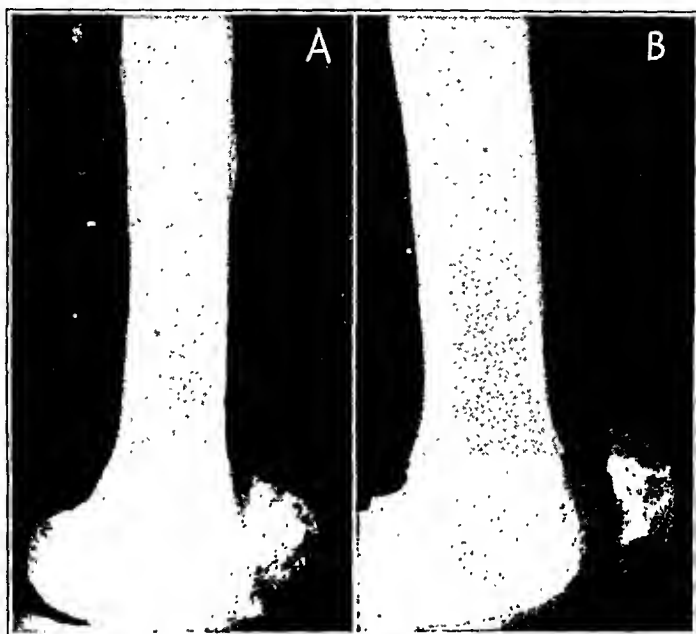


Fig. 3 (case 1).—Response of osteoperiostitis to penicillin therapy. *A*, right femur and patella prior to treatment; *B*, two hundred and forty-five days after start of treatment, illustrating distinct reduction in the original proliferative periostitis. Roentgenograms taken six hundred and eighty-six days after penicillin was begun showed little further change.

Frequent follow-up examinations were carried out in the outpatient department. These revealed a steady, sustained improvement. One hundred and seventeen days after the start of therapy (Feb. 22, 1944) the patient was again admitted to the ward for evaluation of her status. Her weight was now 55.8 Kg. (123 pounds), a total gain of 14.1 Kg. (31 pounds), and she appeared younger and more vivacious; she had had her hair dyed. The edge of the liver extended only 8 cm. below the right costal margin in the midclavicular line and, except for the residual irregular contour of the patellas, examination of the lower extremities revealed no abnormalities.

During the next four months the edge of the liver receded another centimeter, and in June 1944 roentgenograms of the femurs showed considerable improvement over the ones taken prior to treatment; the appearance of the patellas was essen-

tially unchanged (fig. 3 *B*). On Feb. 1, 1945, the liver measured only 5 cm. below the costal margin, and the general status of the patient remained excellent.

The most recent examination, six hundred and eighty-six days after the initiation of penicillin treatment, disclosed a well nourished Negro woman weighing 61.7 Kg. (136 pounds) (fig. 1 *B*). She felt entirely well. The edge of the liver in the midclavicular line was only 3 cm. below the costal margin, and no tenderness was elicited over it or over the femurs or the patellas. Although the flocculation titer of the Eagle test for syphilis was 128 units, the spinal fluid gave no evidence of syphilis. Hematologic studies, including albumin, globulin and hemoglobin determinations and an erythrocyte count, showed that the original improvement had been maintained. Serum alkaline phosphatase activity, elevated at the time of initiation of treatment, was normal. Roentgenograms did not demonstrate significant osseous changes when compared with those last taken.

CASE 2.—A 15 year old white school girl was first admitted to the surgical service of the Johns Hopkins Hospital on April 25, 1944, complaining of a painful, tender lump in the right upper part of her abdomen of two years' duration. She was the third of 13 children, 11 of whom were living. As subsequent investigations brought to light, she had been given some antisyphilitic therapy when about 1 year

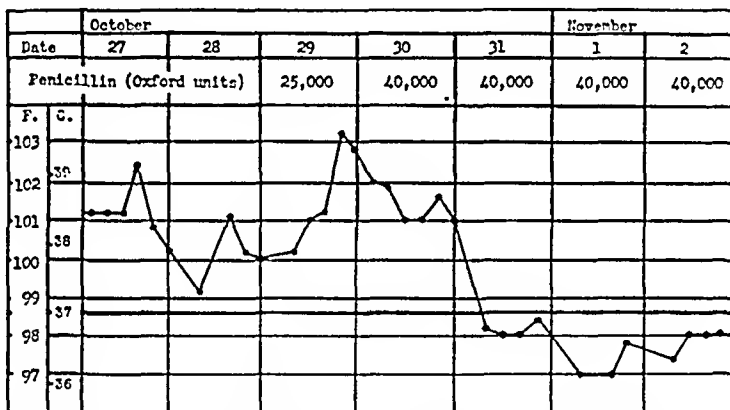


Fig. 4 (case 1).—Response of temperature to penicillin therapy.

of age. Both parents had also had some treatments by injection. The past history was otherwise noncontributory except that menses had not yet begun.

About two years previously, she had felt a spontaneous sharp pain and had noted a firm, tender tumor in the right upper quadrant of her abdomen. Thereafter, although the pain was only occasionally present, the mass continued to increase in size, as observed by herself and her family, and she began to be troubled by a sensation of epigastric fulness for one or two hours after eating. One year prior to her admission to the hospital she had become unable to concentrate on her work or to sleep well and had stopped attending school. Four days before entry she had turned over in bed and had experienced a severe pain on the right side over the abdominal mass, which persisted with movement, or pressure and did not radiate. When she was immobile, her distress would pass entirely away. No jaundice, nausea, vomiting, diarrhea, constipation or melena had been noted, nor had there been weakness or faintness.

On physical examination the patient was an undernourished white girl, pale but not icteric, with poorly developed secondary sex characteristics and a prominent mass in the right upper quadrant of the abdomen. The teeth were carious. Interstitial keratitis was not found (slit lamp examination). Dilated superficial veins were present over the abdomen and the lower part of the thorax. Hepatic

dulness extended from the fourth interspace on the right to the level of the umbilicus; no bruit could be heard, nor could pulsations be distinguished in this region. A distinct nodule, measuring about 5 by 7 cm., firmly attached to, or an integral part of, the anterior surface of the liver, could be seen and felt midway between the costal margin and the umbilicus. The spleen was firm, nontender and easily palpable just above the iliac crest, as illustrated in figure 5 *A*.

Laboratory examinations yielded the following data: The hemoglobin was 9.5 Gm. per hundred cubic centimeters of blood. There were 5,300 leukocytes per cubic millimeter of blood and the differential blood cell count was normal. Bilirubin was present in a concentration of less than 0.8 mg. per hundred cubic centimeters of blood, and no bile was demonstrated in the urine. The albumin-globulin ratio was 0.88, and the total serum protein was 8.81 Gm. per hundred cubic centimeters of blood. The prothrombin time was normal, as was the sulfobromophthalein sodium test. The Eagle flocculation reaction for syphilis was positive.

It was felt by the surgeons that an exploratory operation was indicated in view of the possibility of neoplastic or parasitic disease. On May 1, 1944, cyclopropane

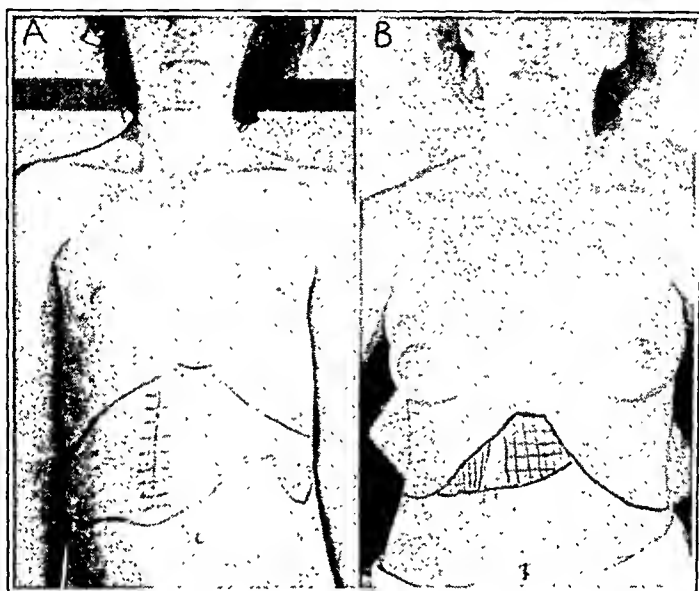


Fig. 5 (case 2).—Response of multiple hepatic gummas to penicillin therapy: *A*, before treatment; *B*, four hundred and ninety-one days after initiation of therapy.

and oxygen anesthesia being used, a laparotomy was performed by Dr. George Duncan. The surface of the right lobe of the liver was described as being studded with large firm nodules, one particularly prominent one causing the visible mass previously noted. The inferior surface of the right lobe had a similar appearance, the process apparently extending through the entire thickness of the organ. The cut surface of the largest nodule, from which a biopsy specimen was taken, was grayish yellow, and the mass itself was rubbery in consistency. The enlarged spleen was granular, with rounded edges. The pathologic report on the microscopic examination of the tissue sections (fig. 6) described large areas of necrosis surrounded by fibrous tissue, occasional scattered solitary tubercles and a slight infiltration of mononuclear cells. Acid-fast stains failed to demonstrate bacilli, and silver impregnation methods did not disclose *Treponema pallidum*. The pathologist's impression was "probable gumma of the liver."

The postoperative course was uneventful, and on May 10 the patient was transferred to the medical service for the penicillin treatment of congenital syphilis and multiple gummas of the liver. Blood serologic tests for syphilis elicited positive reactions; in the Eagle test the flocculation titer was 512 units as shown graphically in figure 7. No cells were seen in the cerebrospinal fluid, and the protein content was normal (19 mg. per hundred cubic centimeters), but the Wassermann reaction was positive with 1.0 cc. of fluid. A negative colloidal mastic curve was reported. The patient's anemia was more profound than before operation. The corrected sedimentation rate (Wintrobe) was 25 mm. per hour. Hippuric acid

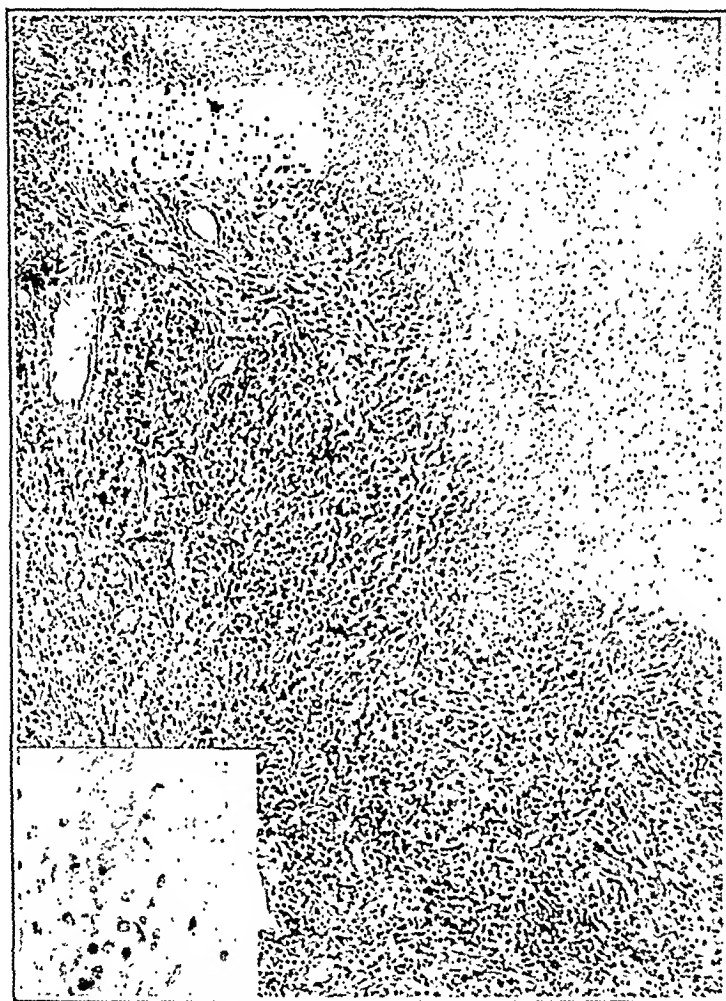


Fig. 6 (case 2).—Biopsy specimen taken prior to penicillin treatment: *A*, low power magnification showing transition from typical area of caseous necrosis to one with epithelioid and infiltrated mononuclear cells, *B*, higher magnification of transition zone ($\times 200$).

synthesis was subnormal (0.62 Gm.), and the sulfobromophthalein sodium test disclosed 12 per cent retention of dye after thirty minutes. Reticulocyte determinations and values for blood nonprotein nitrogen and cholesterol were normal, as were roentgenograms of the long bones. Serum alkaline phosphatase activity was elevated (23.8 Bodansky units per hundred cubic centimeters of serum). Roentgenograms of the thorax and barium sulfate studies of the gastrointestinal tract showed no abnormalities except distortion due to the enlargement of liver and spleen.

Administration of sodium penicillin was begun on May 11. The patient was given 40,000 units in isotonic solution of sodium chloride intramuscularly every three hours for eighty injections, a total of 3,200,000 Oxford units in ten days. The temperature was elevated to 100.4 F (rectal) fifteen hours after the start of treatment. This was interpreted as a possible Herxheimer reaction. She was subsequently afebrile, and therapy was completed without incident. When she was discharged from the ward, distinct general improvement was noticeable. No change was demonstrable in the size of the liver or in that of the spleen, but tenderness over these organs had completely disappeared. The corrected sedimentation rate had fallen to 13 mm. per hour. The total serum protein was slightly decreased to 8.19 Gm. per hundred cubic centimeters of blood, and the albumin-globulin ratio had risen to 1.18. Serum alkaline phosphatase activity was now reported as 17.0 Bodansky units per hundred cubic centimeters of serum.

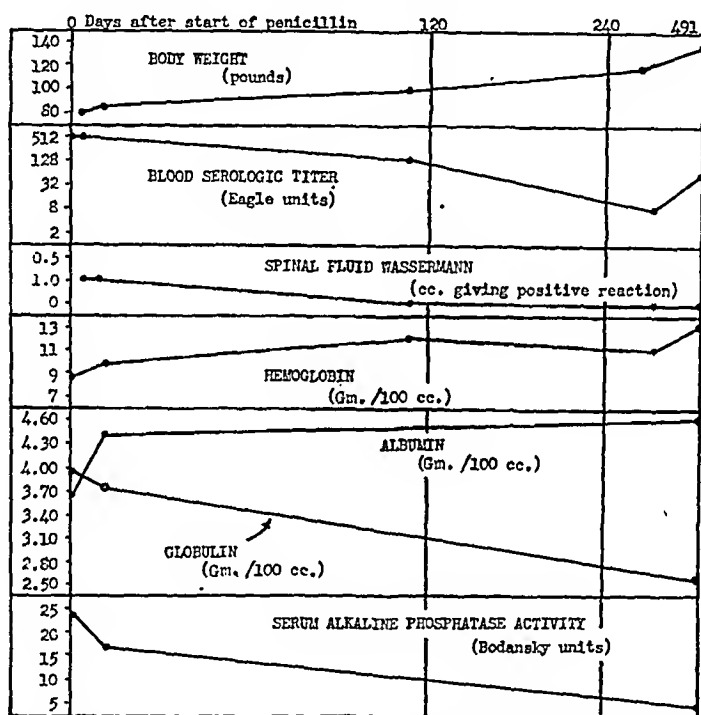


Fig. 7 (case 2).—Improvement following penicillin therapy.

This patient lives at some distance from Baltimore, and visits to the clinic were infrequent. She was next seen in August 1944. The liver then extended 5 cm. below the right costal margin in the midclavicular line. The spleen was no longer palpable. Her color had improved, and she weighed 44.9 Kg. (99 pounds). In the Eagle test for syphilis the flocculation titer had fallen to 128 units, and the Wassermann test of her spinal fluid was negative. In April 1945 the liver extended 4 cm. below the costal margin and could be felt only in the midclavicular line. She remained completely asymptomatic. The Eagle test for syphilis showed a further decrease of titer to 8 units, and the Wassermann test of the spinal fluid remained negative.

On September 13 this patient was again examined. In the four hundred and ninety-one days since the start of treatment her general condition had vastly improved, as shown in figure 5B; menses had begun. The liver was practically normal in size, its edge being palpable between 2 and 3 cm. below the right costal

margin in the midclavicular line. The organ could be percussed out but not definitely felt on the left side of the laparotomy scar. The Eagle test showed the flocculation titer increased to 64 units, but the Wassermann test of the spinal fluid remained negative. The results of chemical and microscopic studies of the blood were all within normal limits, and there was no clinical evidence of hepatic dysfunction.

COMMENT

Active late syphilis of the liver is a condition rarely demonstrated clinically. The initial and essential lesion is the gumma, which arises in a highly localized or focal manner. As emphasized by Hahn,¹ "A focal process, in an organ with the functional reserve and capacity for regeneration of the liver, can rarely be expected to produce symptoms either of hepatic insufficiency or of portal failure. . . ." During the active stage of gummatous involvement fever, pain and tenderness and, as a rule, hepatic enlargement are present; general well-being is usually out of proportion to the duration of symptoms referable to the liver. As with the clinical observations, laboratory and roentgenographic studies do not permit more than a presumptive diagnosis.

Two methods are available for proving the presence of active hepatic gummas. The first and more reliable method is to make a biopsy, a procedure not without risk. The second method is to employ a therapeutic test. Iodides and mercury, bismuth and arsenical preparations in adequate dosages cause the disappearance of signs of gummatous activity in from one to seven days, according to Hahn. He further remarks that "The therapeutic test may be adjudged to be definitely positive only if there is striking change in objective manifestations in direct temporal relationship to antisyphilitic treatment, and *if such change is maintained over a long observation period measured in months, or, preferably, in years.*"

In both the cases reported in this paper, there was clinical evidence of an active gummatous process and definite fulfilment of the criteria of the therapeutic test. In case 2 biopsy further substantiated the diagnosis.

The total doses of penicillin employed were 920,000 and 3,200,000 Oxford units. In the first case dramatic results were obtained following an initial course of only 320,000 units. That visceral gummas should respond to this antibiotic substance is to be expected in the light of recent work on benign late syphilitic lesions in locations accessible to inspection.² Observations extending over six hundred and eighty-six

1. Hahn, R. D.: Syphilis of the Liver, *Am. J. Syph., Gonorr. & Ven. Dis.* **27**:529-562 (Sept.) 1943.

2. Dexter, D. D., and Tucker, H. A.: Penicillin Treatment of Benign Late Syphilis: A Report of Twenty-One Cases, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**: 211-226 (May) 1946.

and four hundred and ninety-one days in the 2 cases reported in this paper have not disclosed evidence of relapse, except for a rise of the serum flocculation titer in each. These data suggest that penicillin is at least as effective in the treatment of visceral gummas as the other forms of antisymphilitic treatment and offers the additional advantage of almost complete lack of toxicity, a factor of some importance when disease of the liver is present.³

The response of the osseous lesions in case 1 was satisfactory from the standpoint of immediate relief of symptoms, and the roentgenographic evidence of resolution of the proliferative process was convincing. Serum alkaline phosphatase activity fell as proliferative activity declined. Skeletal abnormalities were not demonstrated in case 2, however, and no adequate explanation for the increased alkaline phosphatase activity is forthcoming.

From the laboratory standpoint it is noteworthy that the results of spinal fluid tests became negative after the administration of penicillin; the results of blood serologic tests were less affected. Each patient had hyperproteinemia with an absolute increase in the globulin fraction; sustained reversal of the albumin-globulin ratio to normal was demonstrated in each. Other laboratory findings, such as the hemoglobin content, and erythrocyte determinations likewise paralleled the general clinical improvement.

SUMMARY

Acquired benign late syphilis (gummas) of the liver and osseous system (case 1) and multiple hepatic gummas due to congenital syphilis (case 2) were diagnosed clinically. Both diagnoses were substantiated by therapeutic tests and the second also by biopsy.

The patients received 920,000 and 3,200,000 Oxford units, respectively, of commercial sodium penicillin intramuscularly, with dramatic alleviation of acute symptoms and sustained objective and subjective improvement over observation periods of six hundred and eighty-six and four hundred and ninety-one days.

These results show that visceral gummas heal under treatment with commercial penicillin mixtures at least as well as they do under other forms of antisymphilitic treatment. The apparently nontoxic properties of penicillin recommend it particularly in cases in which disease of the liver is present.

3. Moore, J. E.: *The Modern Treatment of Syphilis*, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1945, p. 304.

Progress in Internal Medicine

GASTROENTEROLOGY

A Review of the Literature from July 1944 to June 1945

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AND

SAMUEL N. MAIMON, M.D.

CHICAGO

(Concluded from Page 250)

DUODENUM

Congenital Anomalies.—Sumner and Morris²¹⁷ report a case in which duodenal atresia in a newborn infant, diagnosed early, was successfully treated by duodenojejunosomy. In Mosquera's²¹⁸ case the atresia proved fatal at the age of 18 months.

Secretion.—Comfort²¹⁹ reviews the literature of the last thirty years on duodenal content in health and disease and reaches the following conclusions: During fasting the duodenal content of healthy subjects with achlorhydria is alkaline; in those with acid-secreting stomachs it is acid both in the fasting state and after meals; the reaction of the duodenal content of healthy subjects varies roughly with the amount of acid entering the duodenum; the acidity does not vary greatly between the first and the second portion; drugs, such as atropine sulfate, morphine and the sodium salt of dehydrocholic acid, increase the average p_H of the duodenal content; the antacids used in the treatment of peptic ulcer increase it temporarily; the content of the duodenum in patients with duodenal ulcer is more acid than the normal, the p_H averaging about 2 points lower. Purified secretin evoked secretion of a greater volume of pancreatic juice containing a greater volume of amylase, trypsin and lipase in patients with duodenal ulcer than in normal persons. The secretion of bicarbonate was approximately equal in the two groups.²²⁰

217. Sumner, W. C., and Morris, K. A.: Duodenal Atresia in the Newborn: Case Report, *Am. J. Surg.* **68**:120-123, 1945.

218. Mosquera, J. E.: *Anomalia Intestinal*, *Semana méd.* **51**:1025-1027, 1944.

219. Comfort, M. W.: Acidity of the Duodenal Contents in Health and Disease: A Review of Clinical Investigations, *Gastroenterology* **4**:135-146, 1945.

220. Comfort, M. W., and Osterberg, A. E.: External Pancreatic Secretion in Cases of Duodenal Ulcer, *Gastroenterology* **4**:85-91, 1945.

The interdigestive discharge of duodenal content is considered by Berger and Oppenheim²²¹ to be a cyclic physiologic phenomenon found in so-called resting organs.

Block, Portis and Necheles²²² studied the effect of twenty different detergents on trypsin and found that the inhibitory effect is diminished or abolished by certain substances, such as cream, butter, lecithin, glycerin esters or fatty acids and particularly triacetin.

Injury.—Operation was required to remove a bobbie pin from the duodenum of a 13 month old child.²²³ Trafford²²⁴ reports a retroperitoneal rupture of the duodenum, the mechanism of which was uncertain.

Perforation of the third portion of the duodenum by an atherosclerotic abdominal aorta without aneurysm is reported. The condition is rare, having been described only twice before.²²⁵

Ulcer of the Second Portion.—Crymble²²⁶ reports 4 cases. In 2 of them the lesion was diagnosed only at operation. Weinberger and Rosenthal²²⁷ report a choledochoduodenal fistula due to a duodenal ulcer that penetrated into the common bile duct. The biliary system was well visualized roentgenologically after oral administration of barium sulfate.

Tuberculous Adenitis.—Two instances of duodenal obstruction resulting from tuberculous adenitis have been described.²²⁸

Carcinoma.—There are reported 2 cases of carcinoma of the suprapapillary portion of the duodenum, 1 of the third portion, and 1 case of primary carcinoma of the liver with a spontaneous cholecystoduodenal fistula.²²⁹

221. Berger, W. V., and Oppenheim, E.: The Interdigestive Discharge of Duodenal Content: I. The Rate of Discharge; Four Rhythms, *Gastroenterology* **4**:228-242, 1945.

222. Block, C. L.; Portis, S. A., and Necheles, H.: The Effect of Detergents on the Proteolytic Activity of Trypsin, *Gastroenterology* **1**:45-50, 1944.

223. Latraverse, V., and Ricard, P. M.: Duodenoscopic Removal of a Bobbie-Pin Through a Gastrotomy in a Child Thirteen Months Old, *Canad. M. A. J.* **51**: 560-562, 1944.

224. Trafford, P. A.: Traumatic Retroperitoneal Rupture of the Duodenum, *Lancet* **2**:145-146, 1944.

225. Bernstein, B. M.; Slater, S. R., and Grayzel, D. M.: Perforation of the Aorta into the Alimentary Tract: Case Report, *Clinics* **3**:447-449, 1944.

226. Crymble, P. T.: Ulcer of the Second Part of the Duodenum, *Brit. J. Surg.* **32**:500-502, 1945.

227. Weinberger, J., and Rosenthal, A.: Choledochoduodenal Fistula: Case Report, *Am. J. Roentgenol.* **53**:470-473, 1945.

228. Marshak, R. H., and Dreiling, D.: Duodenal Obstruction Due to Tuberculous Lymphadenitis, *Radiology* **44**:495-497, 1945. Ruiz, M.: Estenosis duodenal profunda por ganglios mesentéricos tuberculosos, siendo este el foco Primario, *Medicina, Madrid* (pt. II.) **12**:775-780, 1944.

In Cattell's ²³⁰ experience carcinoma of the ampulla of Vater is more common and less malignant than that of the pancreas. In 18 patients pancreatoduodenal resection was carried out, with 3 deaths (17 per cent). Satisfactory results were obtained in 13. Of these 1 has been well two years, 5 are alive after eighteen months, 4 after one year and 3 are in good condition during the current year of operation.

SMALL INTESTINE (DUODENUM, JEJUNUM, ILEUM)

Review.—Kiefer's ²³¹ review of fifty-five current papers on diseases of the small intestine is excellent.

Anatomy and Anomalies.—Herstone and Freund ²³² in a study of 54 cadavers conclude that there is no anatomic basis for estimating the distance of a small intestinal lesion from the duodenojejunal junction by its position in the peritoneal cavity; the normal variations are too great.

Bremer ²³³ reviews the literature and the theories of the development of diverticula and duplications of the intestinal tract. In the development of the intestinal tube, proliferation of the inner epithelial layer may produce occlusion of the lumen in the fifth week of embryonal life, but usually complete canalization occurs by the twelfth week. Thorlakson ²³⁴ describes a congenital valve of the upper part of the jejunum which was probably due to incomplete disappearance of this embryonal epithelial tissue in a 3 year old child with incomplete intestinal obstruction. Erb and Smith ²³⁵ report 2 cases of atresia of the intestine, multiple in type in one and single in the other. A premature infant with congenital atresia of the ileum, intestinal perforation and peritonitis is reported on together with a 23 month old boy with a five day history of obstruction who was found to have double intussusception

229. Cohn, I.: Carcinoma of the Duodenum: Report of Two Cases in Suprapapillary Portion, Tr. South. S. A. (1943) **55**:54-62, 1944. Shallow, T. A.; Eger, S. A., and Carty, J. B.: Primary Carcinoma of Third Portion of Duodenum, Surgery **16**:939-946, 1944. Pomeranz, R.; Grady, H. G.; Peelen, M., and Magnes, M.: Spontaneous Cholecystoduodenal Fistula in a Patient with a Primary Hepatoma of the Liver, Radiology **43**:582-587, 1944.

230. Cattell, R. B.: Pancreatoduodenal Resection: A Preliminary Report of Eighteen Cases, New England J. Med. **232**:521-526, 1945.

231. Kiefer, E. D.: The Small Intestine: A Review of Current Literature, Gastroenterology **3**:388-398, 1944.

232. Herstone, S. T., and Freund, S.: The Normal Distribution of the Small Intestine, Am. J. Roentgenol. **52**:46-51, 1944.

233. Bremer, J. L.: Diverticula and Duplications of the Intestinal Tract, Arch. Path. **38**:132-140 (Sept.) 1944.

234. Thorlakson, P. H. T.: Report on a Case of Congenital Valvular Obstruction of the Upper Jejunum, Manitoba M. Rev. **24**:354, 1944.

235. Erb, W. H., and Smith, D. C.: Atresia of Small Intestine: Two Case Reports: One Multiple Atresia with Survival, Ann. Surg. **120**:66-72, 1944.

of the bowel.²³⁶ A successful operation in 1 newborn infant with congenital ileal atresia, gangrene, perforation and peritonitis is described.²³⁷

Haxton²³⁸ reports the death of a newborn infant with a congenital anomaly consisting of a grossly distended and congested small bowel ending in a piriform sac. There was no mesenteric fixation to the posterior abdominal wall; the intestine was twisted around a peritoneal fold enclosing the superior mesenteric artery.

Five fatal cases of volvulus in the newborn arising because of congenital defects in the development of the midgut are presented by Buckley and Wells.²³⁹ Steward²⁴⁰ described 2 instances of faulty third stage rotation.

Physiologic Aspects.—In a study of the nervous mechanisms of the muscularis mucosae, King and Robinson²⁴¹ conclude that: 1. The muscularis mucosae of the small and large intestine of the dog is innervated by both cholinergic and adrenergic motor nerves. 2. Meissner's plexus contains ganglion cells the endings of which are cholinergic, also cells with adrenergic endings. 3. No conclusive evidence has been obtained for the presence of an inhibitory neural mechanism of the muscularis mucosae. 4. The rhythmic movements of the muscularis mucosae are basically myogenic but can be initiated or augmented through the nervous mechanism. 5. The muscularis mucosae may play an important mechanical role not directly connected with the processes of secretion and absorption.

Youmans,²⁴² studying the intestinointestinal inhibitory reflex, found that the stimulus by which intestinal motility is inhibited on distention of the bowel is mediated through a long reflex arc involving the dorsal and lumbar segments of the spinal cord. There was no evidence that the vagus nerves contain either afferent or efferent pathways for the

236. Ficarra, B. J., and Degen, W. B.: Congenital Atresia of the Ileum, Spontaneous Perforation and Multiple Intussusception, *Am. J. Surg.* **65**:123-126, 1944.

237. Arnheim, E. E.: Congenital Ileal Atresia with Gangrene, Perforation and Peritonitis in a Newborn Infant: Staged Operations; Obstructive Resection, Ileocolostomy and Excision of Exteriorized Ileum, *Am. J. Dis. Child.* **69**:108-116 (Feb.) 1945.

238. Haxton, H.: Congenital Absence of Continuity Between Small and Large Intestine, with Abnormal Blood-Supply of the Proximal Colon, *Brit. J. Surg.* **32**:540, 1945.

239. Buckley, R. P., and Wells, A. H.: Volvulus in the Newborn, with a Report of Five Fatal Cases, *Minnesota Med.* **27**:916-919, 1944.

240. Steward, J. A.: Faulty Intestinal Rotation: Case Reports, *Am. J. Surg.* **65**:425-429, 1944.

241. King, C. E., and Robinson, M. H.: The Nervous Mechanisms of the Muscularis Mucosae, *Am. J. Physiol.* **143**:325-335, 1945.

242. Youmans, W. B.: The Intestino-Intestinal Inhibitory Reflex, *Gastroenterology* **3**:114-118, 1944.

reflex. Crohn, Olson and Necheles²⁴³ found that anesthetic drugs applied topically to the mucosa inhibit intestinal motility and tone but not gastric motility.

Preoperative administration of usual doses of morphine and scopolamine inhibited motility of the small bowel in 11 patients. Under these conditions spinal anesthesia did not stimulate the small bowel to contract against a mild distending force (balloon of a Miller-Abbott tube).²⁴⁴

Van Liere and his associates²⁴⁵ noted that in dogs premedicated with cocaine and then subjected either to simple anoxia or to anemic anoxia there was a statistically significant decrease in the propulsive motility of the small intestine.

McGee and Hastings²⁴⁶ confirmed the relative hypotonicity of certain specimens obtained from the fasting human jejunum by intubation, but found that later specimens were isotonic, suggesting that the hypotonicity of the initial specimens is attributable to the admixture of saliva and other hypotonic solutions occasioned by the intubation procedure.

Hormones.—The gastrointestinal mucosa produces nine endocrine principles. The existence of eight of these is unchallenged, although they do not seem vital for the maintenance of life. The following hormones have been identified by physiologic methods: secretin, cholecystikinin and enterogastrone. Enterogastrone has three components; one inhibits gastric secretion, a second inhibits the motility of the vagotomized stomach and a third inhibits the motility of the normally innervated stomach.

The existence of gastrin, enterocrinin and pancreozymin has been established by physiologic methods, but the results of the physiologic investigation lack adequate confirmation. Gastrin stimulates gastric juice in a histamine-like manner, while enterocrinin stimulates the secretion of intestinal juice. The existence of villikin and enterocrinin require confirmation. The former is supposed to stimulate the movements of the villi, while the latter stimulates the motility of the intestine.²⁴⁷

243. Crohn, N.; Olson, W. H., and Necheles, H.: The Local Effect of Topical Anesthetic Drugs on the Motility of the Gastrointestinal Tract of the Human and the Dog, *Surg., Gynec. & Obst.* **79**:41-49, 1944.

244. Helm, J. D., and Ingelfinger, F. J.: The Effect of Spinal Anesthesia on the Motility of the Small Intestine, *Surg., Gynec. & Obst.* **79**:553-556, 1944.

245. Van Liere, E. J.; Northup, D. W., and Stickney, J. C.: The Effect of Anoxia and Anemic Anoxia on the Motility of the Small Intestine and the Influence of an Epinephrine-Potentiating Agent, *Am. J. Physiol.* **142**:615-620, 1944.

246. McGee, L. C., and Hastings, A. B.: The Osmotic Pressure of Fasting Jejunal Secretions in Man, *Gastroenterology* **4**:243-250, 1945.

Physiologic Effects of Massive Resection.—Prioleau²⁴⁸ reports 2 cases of massive resection of the small intestine. One of the patients with a resection of 260 cm. of small intestine and 31 cm. of sigmoid, finally regained an excellent state of health; the other survived the resection of 354 cm. of small intestine and 40 cm. of sigmoid but died four months later of nutritional disturbances and postoperative complications. In the first case approximately 40 per cent of the small bowel was removed; in the second, about 53 per cent—again illustrating the fact that a resection of more than 50 per cent of the small intestine is incompatible with life. In Holman's²⁴⁹ case of obstruction due to volvulus with mesenteric thrombosis, 20 feet (6 meters) of gangrenous bowel, including 19 feet (5.5 meters) of small bowel, ileum, cecum and ascending colon, was resected, and the patient recovered. The stools were semiformal and slightly pale, and contained a moderate excess of unsplit neutral fat, but not an excess of split fat, and only a few undigested muscle fibers. Elman and Read²⁵⁰ report regional ileitis necessitating removal of all the small intestine except for 3 feet (91.5 cm.) of jejunum just distal to the ligament of Treitz, and also the right half of the colon. The patient gained 50 pounds (22.5 Kg.) of weight and experienced normal bowel function on an unrestricted diet. Cosh²⁵¹ describes thrombosis of the superior mesenteric artery requiring resection of the entire ileum, the lower part of the jejunum and the cecum. The patient survived for one year in spite of intractable diarrhea, vomiting, cramps in the legs and the arms and, finally, tetany with low blood calcium (7.2 mg. per hundred cubic centimeters).

Intubation.—In an excellent paper Miller²⁵² outlines his extensive experience with intestinal intubation, emphasizing the value of this procedure for the study of nutritional problems, drug effects and pathologic function of the intestine. Using the Alnico tip in a Miller-Abbott tube, Mayer was able to pass the tube from the stomach to the duodenum in one to two minutes by guiding the highly magnetic tip through the pylorus with an electromagnet.²⁵³

247. Ivy, A. C.: *The Gastrointestinal Hormones: Their Physiology and Applications*, Tr. & Stud., Coll. Physicians, Philadelphia **12**:101-107, 1944.

248. Prioleau, W. H.: *Massive Resection of the Small Intestine: Report of Two Cases*, Tr. South. S. A. (1943) **55**:84-88, 1944.

249. Holman, C. C.: *Survival After Removal of Twenty Feet of Intestine*, *Lancet* **2**:597-598, 1944.

250. Elman, R., and Read, J. A.: *Nutritional Recovery Following Removal of All but Three Feet of Jejunum and Half of the Colon*, *J. Missouri M. A.* **42**:145-146, 1945.

251. Cosh, J. A.: *Tetany After Extensive Gut Resection*, *Lancet* **2**:596-597, 1944.

252. Miller, T. G.: *Intubation Studies of the Human Small Intestine: XXIV. A Review of a Ten Year Experience*, *Gastroenterology* **3**:141-154, 1944.

253. Mayer, H., Jr.: *Passage of Miller-Abbott Tube Through Pylorus with Aid of Electromagnet*, *U. S. Nav. M. Bull.* **43**:463-466, 1944.

Davis and Hansen²⁵⁴ found that by using the Wangenstein aspiration immediately after operation they decreased the number of days of distention of the abdomen and gas pains. Swallowed air is thought to be the main source of the gas.

Roentgenographic Appearance.—Of 73 patients whose small intestines were studied by Ruffin and his associates,²⁵⁵ 28 of them had normal small intestines; a "deficiency pattern" was detected in the remainder, mild in 12, moderate in 23 and severe in 10. Definite alterations of pattern of the small intestine were common in patients with sprue and frank vitamin B complex deficiency but were present also in apparently normal persons. This work is particularly important because of the demonstration that the so-called deficiency pattern may occur in apparently normal persons who show no laboratory evidence of a deficiency state and the consequent conclusion that minor changes of the pattern of the small intestine should be interpreted with caution.

Volvulus.—Barbosa²⁵⁶ reports that a 20 year old woman with volvulus of the entire small bowel was operated on successfully.

Intussusception.—Several instances of intussusception have been reported: One patient was a 14 year old boy²⁵⁷; a second, a 13 year old girl, who was found at operation to have a small adenocarcinoma of the ileum with intussusception²⁵⁸; in 2 patients a submucosal lipoma of the ileum served as the leader²⁵⁹; in another, a jejunal polyp²⁶⁰; in still another, a Meckel's diverticulum²⁶¹; 2 patients—father and daughter—had intussusception of the small bowel caused by adenocarcinoma and occurring alike in each²⁶²; in 2 patients jejunal intussusception developed through a gastroenterostomy stoma,²⁶³ in one of them retrogradely through a subtotal gastrectomy stoma.²⁶⁴

254. Davis, H. H., and Hansen, T. M.: Investigation of the Cause and Prevention of Gas Pains Following Abdominal Operation, Surgery **17**:492-497, 1945.

255. Ruffin, J. M.; Baylin, G. J., and Cayer, D.: The Clinical Significance of Alteration of the Small Intestine Pattern as Demonstrated by X-Ray, Gastroenterology **4**:289-295, 1945.

256. de Castro Barbosa, J. J.: Volvulus of the Entire Small Intestine and Its Mesentery: Case Report, Am. J. Surg. **64**:400-404, 1944.

257. Cabot Case 31021, New England J. Med. **232**:49-52, 1945.

258. Puppel, I. D., and Morris, L. E., Jr.: Adenocarcinoma of the Ileum in a Girl of Thirteen, Am. J. Surg. **66**:113-115, 1944.

259. Cabot Case 31041, New England J. Med. **232**:113-115, 1945; Cabot Case 31131, *ibid.* **232**:350-353, 1945.

260. Copello, O., and Etala, E.: Polipo de yeyuno: Invaginación intestinal Recidivante, Prensa méd. argent. **31**:2153-2154, 1944.

261. Smith, R.: Volvulus of the Small Intestine due to a Meckel's Diverticulum, Brit. J. Surg. **32**:510-511, 1945.

262. Foster, D. B. E.: Adenocarcinoma of the Small Intestine in Father and Daughter, Brit. M. J. **2**:78-79, 1944.

Herniation and Strangulation.—Goode and Newbern²⁶⁵ report intestinal obstruction due to strangulation of the bowel, which had thrust through a defect in the broad ligament of the uterus. Fatal strangulation of the jejunum occurred when the bowel prolapsed through a genuine aperture of the great omentum.²⁶⁶ An interstitial ventral hernia with distended loops of bowel was detected roentgenologically.²⁶⁷

Mesenteric Vascular Occlusion.—Ficarra²⁶⁸ reports 15 cases of mesenteric vascular occlusion, in 3 of which the condition was treated successfully by intestinal resection. The high mortality (60 to 90 per cent) is attributed to shock.

Foreign Bodies: Obstruction and Perforation.—Ingested foreign bodies can be broadly graded, according to McKechnie,²⁶⁹ into metallic bodies, bones and wood splinters. In 90 cases of foreign body in which the site of perforation was recorded, the break-through occurred in the ileocecal region in 63, including 10 with perforation of Meckel's diverticulum, 10 with perforation of the lower part of the ileum, 10 with perforation of the cecum and 33 with perforation of the appendix. In only 5 cases did perforation occur in the gastroduodenojejunal region. Perforation occurred in the colon in 15, in the hepatic flexure in 3, in the transverse colon in 1, in the splenic flexure in 2, in the descending colon in 1, in the sigmoid in 5, in the rectum in 3. In 7 cases no perforation was found but foreign bodies were in abscesses and various abdominal recesses. A nail swallowed accidentally perforated through the rectum into the perineum and the bladder three days later. Hurwich²⁷⁰ found that in 73 per cent of cases of foreign body perforation occurs about the ileocecal region. In an instance of a toothpick lodged in the right colic gutter, the patient could not recall having swallowed the toothpick.

263. Butler, F. E.; Woolley, I. M., and Burton, W. Y.: Jejunal Intussusception Through a Gastro-Enterostomy Stoma, *Radiology* **44**:498, 1945.

264. McNamara, W. L.: Retrograde Jejuno-gastric Intussusception Through a Subtotal Gastrectomy Stoma, *Ann. Surg.* **120**:207-210, 1944.

265. Goode, T. V., and Newbern, W. R.: Intestinal Obstruction Associated with Defects in the Broad Ligaments of the Uterus: Review of Literature and Case Report, *Am. J. Surg.* **65**:127-132, 1944.

266. Sanes, S., and Postoloff, A. V.: Strangulation of the Small Intestine Due to Prolapse Through an Aperture in the Great Omentum, *Gastroenterology* **3**:30-32, 1944.

267. Gray, W., and Horwitz, M.: Interstitial Ventral Hernia Involving the Small Intestine, *Am. J. Surg.* **66**: 134-135, 1944.

268. Ficarra, B. J.: Mesenteric Vascular Occlusion: A Presentation of Fifteen Cases, *Am. J. Surg.* **66**: 168-177, 1944.

269. McKechnie, W. R.: Perforation of the Intestine by a Swallowed Sharp Foreign Body, *Australian & New Zealand J. Surg.* **13**:265-266, 1944.

270. Hurwich, J. J.: Perforation of the Caecum by a Toothpick, *M. Bull. Vet. Admin.* **21**: 232-233, 1944.

Radley²⁷¹ describes an instance of intestinal obstruction produced when a gallstone which had ulcerated through the gallbladder into the duodenum was arrested in the lower part of the ileum.

Hunt and Bowden²⁷² emphasize that the signs and symptoms are minimal when rupture of the intestine results from nonpenetrating injuries of the abdominal wall. The picture is primarily that of slowly developing generalized peritonitis. In the 5 cases reported the mortality rate was 40 per cent. Similarly in 5 cases in which the ruptured bowel was subjected to operation by Bunch²⁷³ there were 2 deaths.

Telford²⁷⁴ observes that while the mortality from gunshot wounds of the abdomen was 90 per cent in the Civil War, it was still 50 per cent in the recent conflict. In 146 cases of perforating abdominal injuries described by Sloan²⁷⁵ the mortality was 22.6 per cent for the entire group. After the introduction of frequent transfusions and treatment with sulfonamide compounds the rate dropped to 10.1 per cent. Experimental support for the use of sulfonamide compounds is provided by Sarnoff and Poth.²⁷⁶ In an experiment carried out with 15 mongrel dogs, ligation of the venous return from segments of the ileum 50 cm. in length in 8 control animals was always lethal, death occurring from peritonitis in forty-eight hours, whereas, of the 7 dogs similarly operated on but treated with 0.5 Gm. of succinylsulfathiazole per kilogram of body weight per day for ten days before operation, 70 per cent survived indefinitely.

Aneurysm.—Levine and Valk²⁷⁷ report a gastrointestinal hemorrhage in an 18 year old girl which was found at operation to be the result of rupture of an aneurysm of a submucosal vessel in the jejunum.

Diverticula.—Johnson²⁷⁸ describes an instance of multiple diverticula of the first part of the jejunum. One hundred and eighty-seven such

271. Radley, S. B.: Intestinal Obstruction Due to a Gall Stone, *Clin. J.* **73**: 226-227, 1944.

272. Hunt, G. H., and Bowden, J. N.: Rupture of Intestine Caused by Non-penetrating Trauma of the Abdominal Wall: A Report of Cases, *Arch. Surg.* **49**: 321-326 (Nov.) 1944.

273. Bunch, J. R.: Intestinal Perforations Due to Non-Penetrating Abdominal Trauma, *South. M. J.* **37**:717-722, 1944.

274. Telford, D.: Gunshot Wounds of the Abdomen (with Report of a Case), *Canad. M. A. J.* **52**:38-42, 1945.

275. Sloan, H. E.: Perforating Abdominal Injuries, with Special Reference to Reduction in Mortality by the Use of Transfusions and Sulfonamides, *Surg., Gynec. & Obst.* **79**: 337-341, 1944.

276. Sarnoff, S. J., and Poth, E. J.: I. The Protective Action of Succinyl-sulfathiazole Following Simple Venous Occlusion, *Surgery* **16**: 927-931, 1944.

277. Levine, J., and Valk, A. de T.: Aneurysm with Rupture of a Submucosal Artery in the Jejunum: Case Report, *Am. J. Clin. Path.* **14**: 586-589, 1944.

cases are reported in the literature. Walker²⁷⁹ discusses the complications.

Meckel's Diverticulum.—Sibley²⁸⁰ in an excellent paper on Meckel's diverticulum estimates its incidence as about 4 per cent in newborn infants and 1 to 3 per cent in adults. In addition to cysts, fecal fistulas and the intestine prolapsed through the umbilicus, the common signs and symptoms may be divided into the obstructive, the inflammatory and the peptic ulcer type. One of the chief purposes of the paper is to call attention to the frequency with which diverticula containing heterotopic gastric mucosa may produce not only the pain and the bleeding of peptic ulcer but a syndrome somewhat akin to diverticulitis. No inflammation is present. Sibley labels the condition as dyspepsia Meckeli and attributes it to spasm of the bowel resulting from irritation produced by the acid and pepsin.

Of 8 specimens studied by Troll,²⁸¹ 3 contained pancreatic tissue and 6 gastric mucosa; 1 contained both types.

Mottram and Garland²⁸² were able to make a roentgenologic diagnosis of Meckel's diverticulum by means of the retained barium sulfate in 1 case.

Gendel and Beaver²⁸³ report the unique case of a 20 year old soldier with Meckel's diverticulum who had acute appendicitis and nevertheless made an uneventful postoperative recovery.

Regional Ileitis.—Kiefer²⁸⁴ found that regional ileitis occurred seventy times in 100,000 registrants at the Lahey Clinic. In a group of 63 patients subjected to operation, subsequent recurrence of the disease was noted in 12.

In an excellent review Bockus²⁸⁵ discusses the present status of chronic regional enteritis and presents his experience with 19 patients treated surgically; 11 were subjected to ileocolostomy, with 1 death; the remaining 10 are alive, but 50 per cent of them give evidence of

278. Johnson, J. A.: Diverticula of the Jejunum, *Minnesota Med.* **28**:395-396, 1945.

279. Walker, R. M.: The Complications of Acquired Diverticulosis of the Jejunum and Ileum, *Brit. J. Surg.* **32**:457-463, 1945.

280. Sibley, W. L.: Meckel's Diverticulum: Dyspepsia Meckeli from Heterotopic Gastric Mucosa, *Arch. Surg.* **49**:156-166 (Sept.) 1944.

281. Troll, M. M.: Aberrant Pancreatic and Gastric Tissue in the Intestinal Tract, *Arch. Path.* **38**:375-380 (Dec.) 1944.

282. Mottram, M. E., and Garland, L. H.: Meckels Diverticulum, *Am. J. Roentgenol.* **53**:142-146, 1945.

283. Gendel, S., and Beaver, M. G.: An Unusual Case of Meckel's Diverticulum, *Ann. Surg.* **121**:981-983, 1945.

284. Kiefer, E. D.: Regional Ileitis, *Clinics* **3**:506-515, 1944.

285. Bockus, H. L.: Present Status of Chronic Regional or Cicatrizing Enteritis, *J. A. M. A.* **127**:449-456 (Feb. 24) 1945.

recurrence of the stenotic process. Two additional patients underwent resection with anastomosis of normal ileum; a third, with extensive segmental ileitis, was subjected to resection of approximately 5 feet (1.5 meter) of the terminal part of the ileum and the ascending colon followed by ileotransversostomy. Thus of 14 patients subjected to operation, 1 died, and 8 (62 per cent) showed recurrent disease. In 5 cases of ileocolitis, ileosigmoidostomy was carried out with a mortality of 40 per cent—two deaths. One patient died three and three-quarters years later; 2 are alive, four and eight years afterward. In summary, then, of 19 patients subjected to operation, good results were obtained only in 7.

Schepers²⁸⁶ divides the lesion into two components: a primary phase, characterized by (a) a stage of edema of the submucosa and the serosa with dilatation of submucosal lymphatics and hyperemia of juxtamuscular adventitial blood vessels, (b) a stage of plasma cell infiltration of submucosa and serosa, (c) diffuse fibrosis with disappearance of plasma cells except where trapped and (d) healing; a secondary phase, characterized by ulceration, which may be superimposed on any primary phase with corresponding modification of the pathologic process. There are tendencies leading to early or late perforation, fistulation and granuloma formation. The importance of a "neuropathic disturbance" of the myenteric plexuses or of the mesenteric and celiac ganglions is stressed with the suggestion that the original neuropathic lesion is possibly a type of visceral herpes zoster.

Ebrill²⁸⁷ reports a 9 year old girl who underwent a 6 inch (15 cm.) resection of the bowel with recovery. Spellberg and Gray²⁸⁸ describe a 23 year old soldier whose disease was confined to the proximal part of the jejunum and required resection of 12 inches (30.5 cm.) of bowel. The symptoms began two months after a nonpenetrating injury of the abdomen. In a 30 year old Negress described by Rees,²⁸⁹ the proximal part of the jejunum was involved, and complete obstruction was produced at three isolated places.

With regard to treatment, Crohn²⁹⁰ remarks that "my approach to this disease is more and more conservative." The upper part of the intestine, if involved, shows a tendency to heal itself, in contrast with

286. Schepers, G. W. H.: The Pathology of Regional Ileitis, *Am. J. Digest. Dis.* **12**:97-116, 1945.

287. Ebrill, D.: A Case of Regional Enteritis in Childhood, *Brit. J. Surg.* **32**:512-514, 1945.

288. Spellberg, M. A., and Gray, L. W.: Regional Enteritis of the Proximal Jejunum Following Trauma, *Surgery* **17**:343-350, 1945.

289. Rees, V. L.: Regional Jejunitis: Report of an Unusual Case, *Am. J. Surg.* **67**:119-122, 1945.

290. Crohn, B. B.: V. The Use of Sulfonamides in Ileitis, *Gastroenterology* **4**:11-13, 1945.

the terminal part of the ileum where the changes progress to scar formation and eventually to obstruction. Succinylsulfathiazole has proved helpful before and after operation.

Tuberculosis.—Camiel²⁹¹ in a well illustrated paper discusses the direct roentgenographic manifestations of ileocecal tuberculosis. The presence of active pulmonary tuberculosis greatly simplifies the diagnostic problem, especially when the terminal part of the ileum is the only portion of the bowel affected. Richieri²⁹² likewise gives a well illustrated discussion of the disease, and Paul²⁹³ reports 5 cases of stricture, tuberculous in origin in 4 of them and due to regional enteritis in 1.

An unusual case of chronic bleeding from the gastrointestinal tract was attributed at operation to lesions of the small intestine. The pathologist was puzzled by the gross and microscopic pictures, considering tuberculosis and regional enteritis in the differential diagnosis. A guinea pig inoculated revealed tuberculosis.²⁹⁴

Sarcoid.—Watson and his colleagues²⁹⁵ describe two very interesting lesions of the small intestine and mesenteric lymph nodes clinically resembling ileojejunitis or Crohn's disease. The roentgen picture was striking with multiple polyposis-like small defects in the pattern of the mucous membrane. Resection of the affected segments produced marked improvement in each instance. Histologic study showed the widespread epithelioid cell tubercle formation typical of sarcoidosis. No evidence of sarcoid was noted elsewhere. Reexamination of the pathologic material from 21 other cases of regional ileitis failed to demonstrate such lesions. Hence the authors conclude that the two described represent isolated sarcoidosis of the small intestine.

Sprue.—Andersen²⁹⁶ found the Sperry method of determining fecal fat to be the most reliable. A comparison of the chemical and the microscopic method showed a high degree of correlation, indicating that the latter method may be useful for screening outpatients. The daily determination of total fecal fat gives a more accurate picture of

291. Camiel, M. R.: Ileocecal Tuberculosis, *Radiology* **44**:344-351, 1945.

292. Richieri, A.: Tuberculosis intestinal: su tratamiento, *Prensa méd. Argent.* **31**:1647-1658, 1944.

293. Paul, M.: Stenosis of the Small Intestine from the Cicatrization of Isolated Inflammatory Lesions, *Brit. J. Surg.* **32**:371-376, 1945.

294. Cabot Case 30321, *New England J. Med.* **231**:237-242, 1944.

295. Watson, C. J.; Rigler, L. G.; Wangenstein, O. H., and McCartney, J. S.: Isolated Sarcoidosis of the Small Intestine Simulating Non-Specific Ileo-Jejunitis, *Gastroenterology* **4**:30-52, 1945.

296. Andersen, D. H.: Celiac Syndrome: I. Determination of Fat in Feces; Reliability of Two Chemical Methods and of Microscopic Estimate; Excretion of Feces and of Fecal Fat in Normal Children, *Am. J. Dis. Child.* **69**:141-151 (March) 1945.

the fat disturbance in digestion than does that of the neutral fat alone. In a study of the fecal fat of infants and children with congenital pancreatic deficiency Andersen²⁹⁷ found that the amount of fecal fat was decreased when the amount of dietary fat was reduced, the decrease of output being roughly proportional to the decrease of intake. The effect of pancreatin was variable, although the excretion of fat was usually reduced. Andersen concluded that the inefficiency of protein digestion, as well as that of fat digestion, has been inadequately stressed heretofore. An optimal diet for patients with congenital pancreatic insufficiency is suggested: Protein should contribute about 25 per cent of the calories; fat should be low; the carbohydrate content should be high, with starch given in part as cereal and potato if these foods are tolerated clinically. Diamond²⁹⁸ gives a good discussion of chronic diarrhea in children, with considerable attention to pancreatic fibrosis and celiac disease.

Klein and Porter²⁹⁹ describe a 16 year old boy with constant hypoproteinemia, hypocalcemia, flat dextrose tolerance curve and slight, although definite, steatorrhea who was studied for four years. At autopsy these abnormalities were found to be due to tuberculosis of the mesenteric and retroperitoneal lymph nodes. Howat³⁰⁰ discusses the occurrence of a spruelike syndrome characterized by stomatitis and steatorrhea which develops occasionally in the course of dysentery. He suggests that it may be a manifestation of a specific deficiency of the vitamin B complex. A syndrome resembling sprue developed in a patient with intrahepatic jaundice following treatment with oxophenarsine hydrochloride. Recovery occurred.³⁰¹

Benign Tumors.—Collins³⁰² analyzes 18 cases of neurofibroma of the small intestine reported since 1929 and adds 1 case. Hanno and Mensh³⁰³ report a fatal hemorrhage of leiomyoma of the jejunum;

297. Andersen, D. H.: Celiac Syndrome: II. Fecal Excretion in Congenital Pancreatic Deficiency at Various Ages and with Various Diets, with Discussion of the Optimal Diet, *Am. J. Dis. Child.* **69**:221-230 (April) 1945.

298. Diamond, L. K.: Chronic Diarrhea and Its Treatment in Infancy and Childhood, *M. Clin. North America* **28**:1189-1209, 1944.

299. Klein, A., and Porter, W. B.: Intestinal Malabsorption Associated with Tuberculosis of Mesenteric Lymph Nodes, *Arch. Int. Med.* **74**:120-130 (Aug.) 1944.

300. Howat, H. T.: Fatty Diarrhea in Chronic and Relapsing Dysentery, *Lancet* **2**:560-561, 1944.

301. Freis, E. D., and Mater, D. A.: Intrahepatic Obstructive Jaundice Following Mapharsen, with Development of a Spruelike Syndrome, *J. A. M. A.* **126**:892-894 (Dec. 2) 1944.

302. Collins, J. D.: Neurofibroma of the Small Intestine, *Tr. South. S. A.* (1943) **55**:74-83, 1944.

303. Hanno, H. A., and Mensh, M.: Leiomyoma of the Jejunum: Intermittent Melena of Fourteen Years' Duration and Fatal Hemorrhage, *Ann. Surg.* **120**:199-206, 1944.

the patient had experienced twenty known episodes of bleeding over a fourteen year period. Packard³⁰⁴ reports a 16 year old girl suffering for many years from anemia labeled as "secondary" who was found at operation to have a cavernous hemangioma covering roughly 5 inches (12.5 cm.) of the ileum about 14 inches (35.5 cm.) above the cecum.

Carcinoid Tumors.—Ritchie and Stafford³⁰⁵ review the literature on argentaffin tumors and report 11 cases in which the incidence of metastases was 27.2 per cent. Additional cases have been noted.³⁰⁶ Esposito and Stout³⁰⁷ report a plasmocytoma of the jejunum causing repeated intestinal hemorrhages over a period of three years. Laparotomy disclosed six constricting lesions of the small intestine with metastases in the regional lymph nodes.

Malignant Tumors.—Warren³⁰⁸ describes 26 cases of primary cancer of the small intestine as recorded in the files of the Toronto General Hospital in the past sixteen years. Fraser³⁰⁹ likewise, in a well illustrated paper, describes 21 cases of cancer of the small bowel, 12 of adenocarcinoma and 9 of sarcoma. At the Lahey Clinic 7 cases of cancer of the small intestine were seen in a period of seven years.³¹⁰

In 5,000 necropsies Herbut and Manges³¹¹ found 12 cases of melanoma. In 5 of these the cancer involved the small intestine and was metastatic. Twenty-five cases of melanoma of the small intestine were found in the literature; in 9 the growth was considered primary and in 16 metastatic. The authors suggest that in all such cases melanoma is in fact metastatic. Melanoblasts have not been demonstrated in the small bowel.

McDougal³¹² describes a patient with a duodenal ulcer in whom carcinoma of the ileum developed, which was resected surgically. Nel-

304. Packard, G. B.: Hemangioma of the Intestine, *Am. J. Surg.* **67**:556-562, 1945.

305. Ritchie, G., and Stafford, W. T.: Argentaffin Tumors of the Gastrointestinal Tract, *Arch. Path.* **38**:123-127 (Sept.) 1944.

306. Blumgren, J. E.: Malignant Carcinoid Tumors of the Small Intestine: Report of Two Cases, *Minnesota Med.* **27**:620-623, 1944. Stevenson, W. O., and Blanchard, A. J.: Carcinoid Tumour of the Ileum with Metastases in the Mesenteric Lymph Nodes, *Canad. M. A. J.* **51**:259-260, 1944.

307. Esposito, J. J., and Stout, A. P.: Multiple Plasmocytoma of the Jejunum, *Am. J. Roentgenol.* **53**:33-39, 1945.

308. Warren, R. F.: Primary Malignant Tumours of the Small Bowel, *Canad. M. A. J.* **51**:450-457, 1944.

309. Fraser, K.: Malignant Tumors of the Small Intestine: A Review of the Literature and Report of Twenty-One Cases, *Brit. J. Surg.* **32**:479-491, 1945.

310. Ficarra, B. J., and Marshall, S. F.: Primary Carcinoma of the Jejunum, *S. Clin. North America* **25**:713-718, 1945.

311. Herbut, P. A., and Manges, W. E.: Melanoma of the Small Intestine, *Arch. Path.* **39**:22-27 (Jan.) 1945.

312. McDougal, W. J.: Carcinoma of the Small Intestine, *Am. J. Surg.* **66**:119-122, 1944.

son³¹³ adds 2 cases. Warren³¹⁴ describes a small intestinal obstruction produced by a secondary carcinoma from an unknown site. A second obstruction due to an unattached similar carcinoma occurred soon afterward, and the patient died.

A housewife had epigastric distress for one year and melena on two occasions; then acute intestinal obstruction developed. At operation cancerous lymphogranulomatosis of the jejunum and mesenteric lymph nodes was found.³¹⁵

Borak³¹⁶ observed 5 lymphoblastic tumors in different parts of the digestive tract, and Bodenheimer,³¹⁷ a sarcoma 7 cm. in diameter in the wall of the jejunum. Cutler, Stark and Scott³¹⁸ report 5 cases of primary lymphosarcoma of the bowel, complicated by intussusception in 3; the patients were children. Radical surgical extirpation and roentgen therapy were used. The mortality was 80 per cent. Terminal lymphatic leukemia developed in 2 patients.

A lymphangioma of the jejunum resulted in severe anemia from continued loss of blood, as indicated on examination of the feces. At laparotomy the lesion was localized, and apparent cure was obtained.³¹⁹

APPENDIX

Appendicitis.—(a) Etiologic Factors: Bowen,³²⁰ reporting on obstructive appendicitis, states that a stercolith was found in 21 (55.3 per cent) of 38 cases, stenosis in 1 (2.6 per cent), kinks and bends in 4 (10.5 per cent) and spasm (no stercolith) or bend in 12 (31.5 per cent). In 40 of 117 cases of acute inflammation, fecal material was found obstructing the lumen; in 12 of the 40 gangrene was present. On the other hand, of 87 cases with no fecal material in the lumen, gangrene was present in only 20. It seems difficult, therefore, to attribute acute appendicitis to obstruction with resultant increase in intra-appendicular

313. Nelson, H.: Carcinoma of the Ileum, *Minnesota Med.* **28**:396-398, 1945.

314. Warren, R. F.: Small Bowel Obstruction Due to an Unattached Secondary Tumour, *Canad. M. A. J.* **52**:44-47, 1945.

315. Mascheroni, H. A.; Reussi, C., and Clerici, L. E.: Estenosis crónica del yeyunoileon por linfogranulomatosis intestinal, *Arch. argent. de enferm. d. ap. digest. y de la nutrición* **19**:466-478, 1944.

316. Borak, J.: Relationship Between the Lymphoblastic Tumor and the Digestive Tract, *Am. J. Digest. Dis.* **11**:241-244, 1944.

317. Bodenheimer, J. M.: Sarcoma of the Small Intestines: Case Report, *Am. J. Surg.* **66**:404-406, 1944.

318. Cutler, G. D.; Stark, R. B., and Scott, H. W., Jr.: Lymphosarcoma of the Bowel in Childhood, *New England J. Med.* **232**:665-670, 1945.

319. Puppel, I. D., and Morris, L. E., Jr.: Lymphangioma of the Jejunum, *Arch. Path.* **38**:410-412 (Dec.) 1944.

320. Bowen, W. H.: Obstructive Appendicitis, *Brit. J. Surg.* **32**:468-471, 1945.

pressure, necrosis, secondary infection, etc., in all cases; it is clear nevertheless that in many instances obstruction by a fecalith followed presumably by such a sequence of events is causal.

A large calculus in the appendix, believed to be the third on record, is reported by Pilcher.³²¹ Bunch³²² describes 4 instances of chronic obstruction of the appendix with retention of contents producing morbid changes known as mucoid disease of the appendix. In 2 cases there were no symptoms; in the other 2 the appendix was perforated.

(b) Diagnosis: Esguerra Gomez³²³ reviews the shifting opinion regarding the roentgenologic diagnosis of appendical disease and concludes that there is increasing skepticism regarding the occurrence of "chronic appendicitis." Lazarus and Marks³²⁴ report 3 cases of appendical abscess, in which symptoms were mainly referable to the urologic tract. Held³²⁵ in discussing the differential diagnosis of peptic ulcer argues for the existence of chronic appendicular disease as a clinical entity. [The reviewers are not at all convinced by his argument.] A syndrome of somatic nerve root pain frequently confused with appendicitis is discussed by Murray.³²⁶ Procaine hydrochloride block of the affected root relieves the pain at least temporarily. Knapp and Claps³²⁷ report a rare instance of an inflamed appendix incarcerated in a femoral hernia. Buxton and Kurman³²⁸ report the case of a 9 year old boy who on the twenty-eighth day after an appendectomy presented a temperature of 105 F. with coughing and expectoration of purulent bloody material. A bronchocolic fistula was demonstrated by roentgenogram. Two years later, the fistula had closed completely, and the patient was reported normal.

(c) Treatment: Stokes³²⁹ found that acute appendicitis ranked rather high among the infirmities of naval personnel, but that the

321. Pilcher, L. S.: Giant Calculus of the Appendix: Report of a Case, *New England J. Med.* **232**:163-165, 1945.

322. Bunch, G. H.: Mucoid Disease of the Appendix, *Ann. Surg.* **121**:704-709, 1945.

323. Esguerra Gomez, G.: Present Value of Roentgenology in the Diagnosis of Appendicitis, *Am. J. Roentgenol.* **52**:624-636, 1944.

324. Lazarus, J. A., and Marks, M. S.: Urological Manifestations Associated with Chronic Appendiceal Abscess, *Am. J. Surg.* **68**:38-43, 1945.

325. Held, I. W.: The Differential Diagnosis of Peptic Ulcer, *M. Clin. North America* **29**:624-638, 1945.

326. Murray, G.: Root Neuritis Vs. Appendicitis, *Canad. M. A. J.* **51**:309-312, 1944.

327. Knapp, C. S., and Claps, L. V.: Appendicitis Incarcerated in a Femoral Hernia, *Am. J. Surg.* **64**:139-140, 1944.

328. Buxton, R., and Kurman, R. L.: Bronchocolic Fistula, *Am. J. Surg.* **67**:137-139, 1945.

329. Stokes, R. J.: Appendicitis in Naval Personnel: Observations on One Hundred and Nine Cases, *U. S. Nav. M. Bull.* **44**:786-789, 1945.

mortality was 75 per cent less than the average civilian mortality owing, presumably, to earlier operation. Fisher and Burch³³⁰ report on 1,494 patients who were operated on for appendicitis over a four year period at the Brooke General Hospital, with 2 deaths. Of these, 645 had acute simple suppurative appendicitis, 34 acute perforative appendicitis with abscess formation, and 39 acute perforative appendicitis with generalized peritonitis—a total of 718 with acute suppurative appendicitis. Among these there were two deaths. The low mortality rate is attributed to early diagnosis, elimination of purgation and post-operative use of sulfanilamide. McPherson and Kinmonth³³¹ report a series of 730 cases of acute appendicitis with a mortality rate of 2.9 per cent for the whole series, 1.17 per cent for cases of simple acute appendicitis, 15.5 per cent for those complicated with peritonitis and 0.8 per cent for those with appendical masses.

Zaslow³³² in reporting 7 instances of appendical rupture and peritonitis interprets the low temperature (under 100 F. orally) on the third postoperative day and the persistent abdominal distention with or without peristalsis as indicative of a mechanical rather than a paralytic obstruction.

(d) Chemotherapy: Stafford, Beswick and Deeb³³³ review a series of 908 perforated appendixes. During the five year period 1939 to 1944 the mortality rate for perforative appendicitis decreased from 9.2 to 3.4 per cent. This is attributed to the use of sulfonamide compounds.

Kaufman and Mersheimer³³⁴ in a careful analysis of the factors influencing the mortality from appendectomy for acute appendicitis conclude

. . . that many factors have contributed an important share to the reduction of our mortality. Among these is the judicious use of intravenous chlorides, plasma or blood to establish an optimum fluid balance during the pre- and post-operative period. Fluid balance should be established before as well as after operation. The routine use of the McBurney incision has contributed to the

330. Fisher, H. C., and Burch, J. C.: The Treatment of Acute Appendicitis, *South. Med. J.* **38**:255-260, 1944.

331. McPherson, A. G., and Kinmonth, J. B.: Acute Appendicitis and the Appendix Mass, *Brit. J. Surg.* **32**:365-370, 1945.

332. Zaslow, J.: Early Postoperative Mechanical Intestinal Obstruction Following the Removal of a Ruptured, Gangrenous Appendix, *Am. J. Surg.* **65**: 276-280, 1944.

333. Stafford, C. E.; Beswick, J., and Deeb, P. H.: Evaluation of Sulfonamides in the Treatment of Peritonitis of Appendiceal Origin: Review of Nine Hundred and Three Cases of Acute Perforative Appendicitis, *Am. J. Surg.* **64**: 227-234, 1944.

334. Kaufman, L. R., and Mersheimer, W. L.: Sulfonamides in Appendicitis: A Review of Four Hundred and Twelve Consecutive Cases and an Analysis of Fatalities, *Am. J. Surg.* **65**:393-403, 1944.

lowered mortality rate as has been emphasized by many observers. A better understanding of the rôle of oxygen and improved anesthesia technic share in the credit. Lastly, a more widespread understanding on the part of our staff of the fundamental importance of prompt and continuous intestinal decompression by the Wangenstein or Furness suction as well as efficient use of the Miller-Abbott tube are vital factors in the management of acute appendicitis except for the addition of the sulfonamides. Since then, the mortality rate has steadily been reduced so that since this study was completed a further group of over 200 consecutive patients of all types have been operated upon without a death. There is definite evidence of the great value of the local and general use of the sulfonamides in the reduction of the serious complications and mortality in the severe forms of acute appendicitis.

Ochsner and Johnston³³⁵ compare the results obtained in the treatment of appendicitis in the years 1933 and 1943. The use of sulfonamide compounds, the administration of blood and plasma and the routine gastrointestinal decompression have changed the picture. The three complications, localized peritonitis, localized abscess and generalized peritonitis, were found to have been caused in 90 per cent of the cases in both years by the administration of laxatives. Immediate operation is advised for all patients with acute appendicitis whether the appendix is ruptured or unruptured; conservative therapy is indicated for localized inflammatory processes. The sulfonamide drugs are thought to give an added factor of safety.

Aycock and Farris³³⁶ review 1,151 consecutive cases in which appendectomy was performed for acute appendicitis during the last decade. From 1935 to 1940, 600 cases, the mortality rate was 5.2 per cent, whereas from 1940 to 1944, 500 cases, it was 1.2 per cent. The lowering of the rate is attributed largely to the administration of sulfonamide compounds.

Kalisova³³⁷ reports a 5 year old child with retrocecal gangrenous appendicitis. The abdomen contained "thin greenish foul-smelling fluid with gas." Hemolytic streptococci, staphylococci and gram-negative diplococci were isolated. Sodium sulfapyridine (1.0 Gm.) was injected every four hours, without demonstrable improvement. Twenty-four hours later, this was stopped, and treatment with penicillin was instituted, 15,000 units being injected into the abdominal cavity through a catheter every three hours. After the first twenty-four hours, the child began to make a striking recovery, and the gram-positive organisms seen in the abdominal fluid disappeared.

335. Ochsner, A., and Johnston, J. H.: Appendical Peritonitis, *Surgery* **17**: 873-892, 1945.

336. Aycock, T. B., and Farris, E. M.: Appendicitis: The Possible Effects of Sulfonamides on Mortality, *Ann. Surg.* **121**:710-720, 1945.

337. Kalisova, M.: Acute Appendicitis Treated with Penicillin, *Brit. M. J.* **2**:597, 1944.

[In the judgment of the reviewers, chemotherapy is not necessary or indeed justifiable in cases of simple acute appendicitis; when localized or general peritonitis or appendical abscess is present the use of both drugs is indicated, the sulfonamide compound being more effective against the gram-negative organisms and penicillin relatively more effective against the gram-positive ones.³³⁸]

In an excellent experimental study Daniel and Holbrook³³⁹ injected a suspension of hemolytic *Staphylococcus aureus* among the loops of intestine in 25 dogs; 21 died with peritonitis—84.0 per cent. Among 19 dogs given similar injections and treated with the sulfanilamide group of drugs only 9 died with peritonitis—47.4 per cent; among 21 dogs given sulfathiazole 17 died with peritonitis—66.6 per cent; among 24 dogs given sulfadiazine 14 died with peritonitis—58.3 per cent. Penicillin was not tried. Bigger³⁴⁰ has apparently confirmed the observation of Ungar on the synergistic action of penicillin and sulfonamide compounds.

Pseudomyxoma Peritonei.—In 3,087 cases in which appendectomy was performed, mucocele was encountered five times, an incidence of 0.13 per cent. A ruptured mucocele with pseudomyxoma peritonei is described.³⁴¹

Carcinoma.—Chomet³⁴² reports 3 cases of carcinoma of the appendix; in 2 a clinical diagnosis of appendicitis was made; in the third the tumor was removed incidentally at the time of a hysterectomy.

LARGE INTESTINE (CECUM, COLON, RECTUM)

Epidemic Diarrhea of the Newborn.—Campbell³⁴³ analyzes an outbreak of epidemic diarrhea occurring in 50 newborn infants in Australia. The explosive rapidity with which the disease spreads is spectacular. The stools are fluid, resembling yellow water, with no solid constituents. The value of parenteral fluids is great; sulfaguanidine is considered to have a definite beneficial effect. The mortality is higher in premature than in full term infants. The etiologic agent is unknown, and the mode of spread is uncertain, although certain signs suggest that it

338. Palmer, W. L., and Ricketts, W. E.: Chronic Ulcerative Colitis with Generalized Peritonitis and Recovery, *Arch. Surg.* **51**:102-105 (Sept.) 1945.

339. Daniel, R. A., Jr., and Holbrook, T. J.: The Prevention of Staphylococcus Infections of the Peritoneum, *Surgery* **17**:39-46, 1945.

340. Bigger, J. W.: Synergic Action of Penicillin and Sulphonamides, *Lancet* **2**:142-145, 1944.

341. Timoney, F. X.: Ruptured Mucocele of the Appendix with Pseudomyxoma Peritonei, *Am. J. Surg.* **64**:417-419, 1944.

342. Chomet, B.: Carcinoma of Appendix, *Am. J. Clin. Path.* **14**:447-451, 1944.

343. Campbell, K. I.: Report on an Outbreak of Epidemic Diarrhea of the Newborn, *M. J. Australia* **1**:79-84, 1945.

may be air borne. Menchaca³⁴⁴ on the basis of 20 cases concludes that sulfadiazine is efficacious in the treatment of diarrhea of infants.

Virus Diarrhea.—Reimann, Hodges and Price³⁴⁵ describe a mild epidemic disease characterized by anorexia, malaise, diarrhea, nausea and vomiting occurring in October and November of both 1943 and 1944 in Philadelphia. The infection is thought to have been an air-borne one; the etiologic agent is unknown.

Staphylococcic Food Poisoning.—An outbreak of food poisoning due to infected ham is described. The possible source of the infection was a food handler who carried an enterotoxin-producing strain of *Staphylococcus aureus* in his nasopharynx.³⁴⁶

Salmonella Infections.—Stewart and Slack³⁴⁷ report a mild outbreak of food poisoning due to *Salmonella Oranienburg* present in veal solid. Two hundred men were affected. The source was not determined. Greifinger and Silberstein³⁴⁸ report 115 cases of acute gastroenteritis in military personnel. *S. Oranienburg* was isolated in 86.9 per cent, *S. typhimurium* in 23.5 per cent and *S. anatus* in 38.2 per cent. *S. Oranienburg* persisted in the feces for thirteen weeks, *S. anatus* for eleven weeks and *S. typhimurium* for five weeks. Succinylsulfathiazole in adequate dosage had a bacteriostatic effect on the first two, aiding in the termination of the carrier state.

Lieberman³⁴⁹ attributes an attack of acute bacillary dysentery to *Bacillus alkalescens* (*Shigella alkalescens*). In the feces of 3 patients with continued fever of the enteric type Raeburn found an organism resembling and probably identical with *Bacillus faecalis alcaligenes* (*Alkaligenes faecalis*).³⁵⁰ Silverman and Leslie³⁵¹ report 4 instances of intestinal infection simulating chronic bacillary dysentery but pro-

344. Menchaca, F. J.: Sulfadiazine in the Treatment of Diarrhea in Children, *Am. J. Dis. Child.* **68**:5-6 (July) 1944.

345. Reimann, H. A.; Hodges, J. H., and Price, A. H.: Epidemic Diarrhea, Nausea and Vomiting of Unknown Cause, *J. A. M. A.* **127**:1-6 (Jan. 6) 1945.

346. Rutherford, P. S., and Crowson, C. N.: The Bacteriology of an Epidemic of Staphylococcal Food Poisoning, *Canad. M. A. J.* **52**:19-20, 1945.

347. Stewart, J. K., and Slack, J. M.: *Salmonella* Food Poisoning, *Bull. U. S. Army M. Dept.*, 1945, no 88, pp. 120-122.

348. Greifinger, W., and Silberstein, J. K.: *Salmonella* Food Infection in Military Personnel: An Outbreak Caused by *S. Oranienburg*, *S. Typhi Murium* and *S. Anatum*, *J. Lab. & Clin. Med.* **29**:1042-1053, 1944.

349. Lieberman, W.: Acute Bacillary Dysentery Due to *Bacillus Alkalescens*, *Rev. Gastroenterol.* **12**:123-125, 1945.

350. Raeburn, C.: An Enteric-like Infection Due to *B. Faecalis Alkaligenes*, *J. Roy. Army M. Corp.* **63**:151-152, 1944.

351. Silverman, D. N., and Leslie, A.: The Simulation of Chronic Bacterial Dysentery by Paratyphoid B. Infection, *Gastroenterology* **4**:53-60, 1945.

duced by *Bacillus paratyphosus* B (*Salmonella paratyphi* B). Wang³⁵² tested 30 samples of Chinese soybean sauce made with water from shallow wells in China and found that 35 per cent were contaminated with *Escherichia coli*, *Eberthella typhosa*, *Shigella dysenteriae* or other *Salmonellae*.

Barnes³⁵³ presents evidence that certain members of the paracolon, *Proteus* and *Pseudomonas* groups of micro-organisms may be able, under certain conditions, to initiate outbreaks of gastroenteritis, diarrhea or dysentery-like disturbances. He further suggests that the terms "paratyphoid bacilli" and "paratyphoid fever" should be discarded in favor of "salmonellas" and "salmonelloses," respectively, since the former names are "restricted," ambiguous and obsolete." A list of the types of salmonellas known at the present time is included.³⁵⁴ Michael and Harris³⁵⁵ suggest that normal nonpathogenic organisms of the paracolon bacilli group may cause acute gastroenteritis under conditions of poor sanitation.

A diet of whole wheat and whole dried milk was shown to promote a higher survival rate among W-Swiss mice subjected to *Salmonella enteritidis* infections than that given by a synthetic diet. The unknown nutritional factors present in whole wheat are absent or negligible in dried whole milk.³⁵⁶

Bacterial Dysentery.—(a) Incidence: In the Navy the curve of hospitalization rates for diarrheal disease decreased gradually from 84.38 in 1882 to 10.01 in 1913. Definite progress since 1913 can be demonstrated only in the typhoid-paratyphoid, or salmonella, infections. Since 1922 the admission rates for chronic diarrheal diseases, cause unspecified, have definitely increased. Similarly, since 1914 the admission rates for diarrheal diseases caused by food-borne organisms, toxins or poisons have definitely increased. Further progress is thought to depend on the development of specific immunization against organisms causing bacillary dysentery and all food-borne organisms and toxins.³⁵⁷ Of impor-

352. Wang, C. I.: Chinese Soy Bean Sauce as a Transmitting Agent of Bacterial Gastrointestinal Infections, *Am. J. Trop. Med.* **25**:47-50, 1945.

353. Barnes, L. A.: Pathogenic Enteric Bacilli: Paracolon, *Proteus* and *Pseudomonas* Groups, *U. S. Nav. M. Bull.* **43**:707-716, 1944.

354. Barnes, L. A.: Pathogenic Enteric Bacilli: The *Salmonella* Group, *U. S. Nav. M. Bull.* **43**:939-949, 1944.

355. Michael, M., Jr., and Harris, V. T.: Paracolon Bacilli: A Study of Fifty-Three Isolated Strains, with a Note on Pathogenicity, *War Med.* **7**:108-115 (Feb.) 1945.

356. Schneider, H. A., and Webster, L. T.: Nutrition of the Host and Natural Resistance to Infection, *J. Exper. Med.* **81**:359-384, 1945.

357. Smiley, D. F., and Raskin, H. A.: Diarrheal Diseases in the Navy: The Navy's Experience, 1882-1942, *U. S. Nav. M. Bull.* **44**:267-283, 1945.

tance in this respect is the work of Cooper and his associates.³⁵⁸ Blood obtained from children immunized with killed suspensions of dysentery bacilli showed an increase in passive mouse-protective power ranging from thirteen fold to six hundred and forty-five fold. This protective power decreased gradually but was present in an appreciable degree after twenty-four weeks. Homologous was always greater than heterologous immunity. The results suggest that active immunization with combined antigens may offer protection for a few weeks or months. Volunteers immunized with the purified specific antigen of type V *Shigella paradysenteriae* (Flexner) by Perlman and co-workers³⁵⁹ had a high titer of bacterial agglutinins and mouse-protective antibodies. The titer fell moderately in six months and then rose fairly well in response to a small recall dose of the antigen.

Hurevitz³⁶⁰ concludes that, "of all noncombat casualties, bacillary dysentery is proving one of the most significant causes for disability among troops in this war, as it has in all other wars." Sanitary discipline is the most important factor in its prevention. Of 1,120 patients with diarrhea admitted to an overseas station hospital between May 1 and November 1, 567 had stool cultures positive for bacillary dysentery, 409 (69.8 per cent) harboring *Shigella paradysenteriae*. Pot³⁶¹ found that in Curaçao bacillary dysentery is one of the most frequent infectious diseases, 429 cultures of various strains of *Shigella paradysenteriae* having been obtained in 2,753 stool examinations.

(b) Transmission: In an evaluation of the various factors in the cases of dysentery seen in the South Pacific, Calarco³⁶² considers the common fly as "the main vector in the transmission of bacillary dysentery" and contaminated food as the chief source of amebic dysentery, although the importance of all sanitary measures is emphasized. Sulfonamide compounds are recommended for the therapy of severe bacillary dysentery, emetin hydrochloride and carbarsone for that of amebic dysentery. The difficulties presented by combined infections may be rather great.

358. Cooper, M. L.; Tepper, J., and Keller, H. M.: Active Immunization of Children with *Shigella Paradysenteriae* and *Shigella Sonnei*, *Proc. Central Soc. Clin. Research* **17**:68, 1944.

359. Perlman, E.; Binkley, F., and Goebel, W. F.: Studies on the Flexner Group of Dysentery Bacilli: III. Antibody Response in Man Following the Administration of the Specific Antigen of Type V *Shigella Paradysenteriae* (Flexner), *J. Exper. Med.* **81**:349-358, 1945.

360. Hurevitz, H. M.: Bacillary Dysentery, *War Med.* **6**:247-250 (Oct.) 1944.

361. Pot, A. W.: Bacillary Dysentery in Curaçao, Netherlands West Indies, *Am. J. Digest. Dis.* **12**:70-73, 1945.

362. Calarco, J. J.: The Dysenteries, *M. Clin. North America* **28**:1497-1508, 1944.

In North Africa dysentery bacilli were found by Stewart³⁶³ to be viable in feces eleven days after passage under natural conditions of drying. In rain water Flexner organisms were viable for thirty-eight days. Carriers in the native population of North Africa were found to constitute an important source of infection, and flies, an important means of transmission. It was shown that flies could transmit bacilli from dried feces to the culture plates for as long as eleven to twelve days after passage of the feces.

Fairbrother³⁶⁴ reports that *Shigella dysenteriae* was isolated from the feces on 245 occasions in a group of 2,500 apparently healthy Italian prisoners of war, an incidence of carriers of 10 per cent. All carriers were given a routine course of sulfaguanidine, 6 Gm. three times on the first day and 3 Gm. three times daily for the next five days, making a total dose of 63 Gm. in six days. The treatment appeared to be successful in 227 cases; in the 16 failures the types found were Flexner (12 cases), Shiga (2) and Sonne (2). In the majority of these cases the response to the second course of sulfaguanidine was satisfactory. Jacoby and associates³⁶⁵ emphasize the importance of control of flies, careful bacteriologic examination of food handlers, strict care in the preparation of all foods containing meat, milk, eggs and mayonnaise, and chlorination of water. A combination of sulfathiazole and sulfaguanidine is considered most effective in treatment; it lowered the period of hospitalization from 7.2 to 5.0 days, and cleared 96 per cent of the infections within six days, for the 47 patients so treated.

Sandweiss³⁶⁶ has analyzed the hazard presented by carriers of dysentery shigellas who serve as food handlers. He pleads for a comprehensive national program of prevention of dysentery, for more rigid rules in the examination of food handlers and for more frequent follow-ups of all persons found to be carriers.

(c) Treatment: In War Department Technical Bulletin no. 119, in the section dealing with the treatment of bacillary dysentery emphasis is laid on hydration and chemotherapy (sulfadiazine being suggested as the drug of choice, and sulfathiazole, succinylsulfathiazole and sulfaguanidine as less satisfactory substitutes). Penicillin is not effective. Serum therapy is apparently of little value. Rest in bed and isolation

363. Stewart, W.: On the Viability and Transmission of Dysentery Bacilli by Flies in North Africa, *J. Roy. Army M. Corp.* **63**:42-46, 1944.

364. Fairbrother, R. W.: The Control of Bacillary Dysentery, *Brit. M. J.* **2**:489-492, 1944.

365. Jacoby, A. H.; Loudon, J. R.; Wyne, P. S., and Failmezger, T. R.: The Diarrhea Problem in a New Guinea Base, *Bull. U. S. Army M. Dept.*, 1945, no. 86, pp. 70-78.

366. Sandweiss, D. J.: Diarrhea and Bacillary Dysentery in Detroit: A Study of the Effect of Sulfathalidine on Bacillary Dysentery Carriers, *Clinics* **3**:553-576, 1944.

are important. Purgation and enemas are contraindicated. Strict attention to prophylactic measures, such as isolation, sewage disposal, disinfection of bedding and dishes, maintenance of a proper food and water supply, instruction of food handlers, fly control, screening and the use of DDT spray are emphasized. The practical value of immunization has not been demonstrated.³⁶⁷

Felsen³⁶⁸ summarizes the present knowledge of the action of sulfonamide compounds and advises that an initial dose of 0.25 Gm. per kilogram of body weight be given during the first twenty-four hours in divided doses, one every four hours, and that thereafter half of this dose be given daily until the symptoms recede and for a minimum of several days. Beneficial effects in varying degrees are obtained with both the poorly and the readily absorbed sulfonamide drugs. There is some evidence that a combination of these two types may be more desirable for general use than either type alone. Scott³⁶⁹ finds that for patients with mild bacillary dysentery the mean length of stay in the hospital is decreased from 12.7 to 11.6 days by the use of sulfaguandine and the discontinuation of saline purgation. It is not clear how much of the slight decrease is to be attributed to the drug and how much to the discontinuance of purgation. Ferriman and Mackenzie³⁷⁰ compare the effects of different sulfonamide compounds in 56 cases and find that the average time of recovery is three to six days (18 cases) for sulfanilamide, three to four days (18 cases) with sulfaguandine and two to seven days (20 cases) with sulfathiazole. In vitro studies of the action of various sulfonamide compounds on *Shigella dysenteriae* afford evidence that sulfathiazole and sulfadiazine give the best results, while sulfaguandine is relatively ineffective.³⁷¹

On the other hand, Fortune and Ferris³⁷² on the basis of an experience with 2,810 cases of bacillary dysentery in New Guinea consider sulfaguandine administered in a dose of at least 90 Gm. over a period of seven days the treatment of choice when the infection is in an early stage.

367. Bacillary Dysentery, United States War Department, Technical Bulletin (TB Med 119), War Med. 7:36-39 (Jan.) 1945.

368. Felsen, J.: VII. Effects of the Sulfonamides in Bacillary Dysentery, *Gastroenterology* 4:14-16, 1945.

369. Scott, R. B.: On the Effect of Sulphaguandine in Acute Bacillary Dysentery, *J. Roy. Army M. Corp.* 64:159-162, 1945.

370. Ferriman, D. G., and Mackenzie, G. K.: Comparison of Sulphonamides in Bacillary Dysentery, *Lancet* 2:687-688, 1944.

371. Beemer, A. M. A., and Fairbrother, R. W.: The In-Vitro Activity of Various Sulphonamides on *Bact. Dysenteriae*, *J. Path. & Bact.* 56:567-569, 1944.

372. Fortune, C., and Ferris, A. A.: Diarrhoeal Diseases in New Guinea, *M. J. Australia* 1:337-344, 1945.

(d) Bacteriophage: Morton and Engley³⁷³ review the status of bacteriophage in bacillary dysentery and conclude that while the evidence regarding its therapeutic use is inconclusive, the results in prophylaxis are encouraging.

(e) Streptomycin: Reimann and his co-workers³⁷⁴ report that oral administration of streptomycin suppresses the growth of *Escherichia coli* and *Eberthella typhosa* (*Salmonella typhi*) in the feces.

(f) Typhoid with Perforation: Scott and Ortner³⁷⁵ describe successive multiple intestinal perforations from typhoid occurring in an 11 year old boy. Administration of sulfathiazole and succinylsulfathiazole in conjunction with the surgical repair of the perforation resulted in recovery. A similar case is reported by Dubrow.³⁷⁶

Parasitic Dysentery.—The excellent manual of tropical medicine prepared by Mackie, Hunter and Worth³⁷⁷ under the auspices of the National Research Council is well worth the study of all interested in this field. Turner,³⁷⁸ who has had extensive experience with tropical and parasitic medicine, gives an excellent review of the various types of dysentery.

Bailey³⁷⁹ calls attention to the prevalence of intestinal parasites throughout the Southeastern United States. The soil and the climate of Kentucky are particularly conducive to unusually heavy infection. Elimination of infection may be accomplished through proper drainage of the soil and proper care of the latrines of the community. *Ascaris lumbricoides* is the most common infectious agent in children; *Trichuris trichiura* and *Necator americanus*, the most prevalent in adults. Treatment is not highly successful, because complete elimination of the infection is difficult. Nevertheless, the infection may be reduced sufficiently to free the patient from disease. Of 1,452 patients examined in an

373. Morton, H. E., and Engley, F. B.: Dysentery Bacteriophage: Review of the Literature on Its Prophylactic and Therapeutic Uses in Man and in Experimental Infections in Animals, *J. A. M. A.* **127**:584-591 (March 10) 1945.

374. Reimann, H. A.; Elias, W. F., and Price, A. H.: Streptomycin for Typhoid: A Pharmacologic Study, *J. A. M. A.* **128**:175-180 (May 19) 1945.

375. Scott, E. P., and Ortner, A. B.: Typhoid: Successive Intestinal Perforations with Recovery, *Am. J. Dis. Child.* **68**:119-121 (Aug.) 1944.

376. Dubrow, A. A.: Perforation of the Intestine Due to Typhoid, *J. A. M. A.* **126**:495-496 (Oct. 21) 1944.

377. Mackie, T. T.; Hunter, G. W., and Worth, C. B.: A Manual of Tropical Medicine, National Research Council, Division of Medical Sciences, Philadelphia, W. B. Saunders Company, 1945.

378. Turner, E. L.: The Dysenteries, *Ohio State M. J.* **40**:1133-1139, 1944; Amebiasis; Other Intestinal Protozoal Infections; Helminthous Dysentery, *Kentucky M. J.* **42**:135-143, 1944; Bacillary Dysentery, *ibid.* **42**:95-101, 1944.

379. Bailey, W. C.: A Study of the Incidence and Treatment of Intestinal Parasites in Southeastern Kentucky, *South. M. J.* **37**:407-409, 1944.

institution for patients with tuberculosis, 64 (4.4 per cent) harbored parasites: *Strongyloides*, *N. americanus*, *Endamoeba coli*, *Ascaris lumbricoides*, *T. trichiura* and *Hymenolepis nana*.³⁸⁰

Of 161 children infected with multiple parasites, 119 (74 per cent) were brought to the hospital for other conditions, although the diseases of 26 per cent later were shown to be due to parasitism alone. Vomiting, vomiting of worms, fever, diarrhea, anorexia, abdominal pain and passage of worms are the most frequent manifestations. Eosinophilia occurred in less than 20 per cent of the patients. Hexylresorcinol was the most effective vermifuge for ascariasis and tetrachloroethylene the most effective for ancylostomiasis. Sanitary disposal of feces is vital for the prevention of infection.³⁸¹

Markell³⁸² analyzes the results of 2,388 examinations of stools made by means of the direct centrifugal flotation method of Faust and 1,371 examinations of wet smears in New Zealand. Intestinal parasites were found in 28 per cent. The zinc sulfate technic combined with iron-hematoxylin staining of smears demonstrated an average of 36 per cent of the *E. histolytica* infections with a single examination, 59 per cent with two examinations and up to 93 per cent with six examinations. With three examinations 85 per cent of the nonpathogenic amebic infections were demonstrated. Only 20 per cent of the patients entered the hospital with gastrointestinal complaints. Of the total, 8.46 per cent had hookworm infection; 8.09 per cent, *E. histolytica* infection, and 22.15 per cent, *E. nana*—an incidence about twice the average found within the continental United States. A survey of intestinal parasites among 125 Melanesians disclosed a high incidence of hookworm infection together with a moderately high incidence of infections with *A. lumbricoides* and *T. trichiura*.³⁸³

Wirts and Tallant³⁸⁴ in the Middle East found that approximately 12 per cent of patients harbored one or more forms of intestinal parasite and 23 per cent a bacillary pathogen, predominantly *Shigella paradysenteriae* Flexner.

380. Habeeb, W. J.: Human Intestinal Parasites in a West Virginia Tuberculosis Institution, South. M. J. **37**:701-703, 1944.

381. Einhorn, N. H.; Miller, J. F., and Whittier, L.: Intestinal Polyparasitism: Clinical Survey of One Hundred and Sixty-One Cases of Infection with Multiple Intestinal Parasites in Children, Am. J. Dis. Child. **69**:350-358 (June) 1945.

382. Markell, E. K.: Intestinal Parasitic Infections in a Naval Hospital in New Zealand, U. S. Nav. M. Bull. **44**:65-68, 1945.

383. Russell, H. K., and Scott, J. O.: Intestinal Parasites Among Melanesians, U. S. Nav. M. Bull. **44**:727-728, 1945.

384. Wirts, C. W., Jr., and Tallant, E. J.: Dysentery in American Troops in the Middle East, Am. J. Digest. Dis. **11**:252-255, 1944.

(a) Amebiasis: Craig,³⁸⁵ the outstanding authority in this field, has published a new book on the causation, the diagnosis and the treatment of amebiasis. While it cannot be reviewed here, it can, nevertheless, be recommended most highly.

In a splendid experimental study Chang³⁸⁶ has shown that a strain of *E. histolytica* may lose its infectivity and some of its pathogenicity for kittens after a long period of cultivation without encystment, that the infectivity of the noninfective cultural strains can be restored by encystment, that the presence of a virulent bacterial flora may not increase the infectivity for kittens of noninfective cultural strains of *E. histolytica* and that in studying the virulence of cultural strains of *E. histolytica*, distinction should be made between infectivity and pathogenicity.

Of 112 patients admitted to a military center for patients with tropical diseases in England, who were suffering from dysentery or its effects, 33 were found to have amebiasis. Of these, only 7 had had recent diarrhea and in 14 diarrhea had never been prominent. Emetine bismuth iodide given orally and emetine bismuth iodide with chiniöfon administered rectally gave the most permanent cures.³⁸⁷

Browne, McHardy and Spellberg³⁸⁸ studied 3,984 ambulatory patients with amebiasis. In office patients the incidence was 14.1 per cent, in contrast with 5.2 per cent in hospital patients. Roentgen examination (barium sulfate enema) disclosed changes consistent with amebic colitis in 35.5 per cent. In 42.2 per cent of the patients with active dysentery ulcers were seen on proctoscopic examination. Taubenhaus³⁸⁹ emphasizes the importance of amebiasis as a cause of recurrent abdominal pain and mild diarrhea.

In the dysentery ward of a forward British field hospital in an undisclosed location 2,114 patients with diarrhea were admitted, 370 of whom were found to have bacillary dysentery (7, or 1.8 per cent, died) and 701 amebic dysentery (10, or 1.4 per cent, died). Four of the 10 had perforation and 1 gangrene of the descending colon. There were 68 patients with amebic hepatitis and amebic abscess. Almost half of the

385. Craig, C. F.: *The Etiology, Diagnosis and Treatment of Amebiasis*, Baltimore, Williams & Wilkins Company, 1944.

386. Chang, S. L.: *Studies on Entamoeba Histolytica: V. On the Decrease in Infectivity and Pathogenicity for Kittens of E. Histolytica During Prolonged in Vitro Cultivation and Restoration of These Characters Following Encystment and Direct Animal Passage*, *J. Infect. Dis.* **76**:126-134, 1945.

387. Bomford, R. R.: *Chronic Amoebiasis in Soldiers*, *J. Roy. Army M. Corp.* **83**:279-283, 1944.

388. Browne, D. C.; McHardy, G., and Spellberg, M. A.: *Statistical Evaluation of Amebiasis*, *Gastroenterology* **4**:154-163, 1945.

389. Taubenhaus, L. J.: *Amebiasis as Cause of Recurrent Abdominal Pain: Report of Cases*, *U. S. Nav. M. Bull.* **43**:527-531, 1944.

patients suffered from a nonspecific diarrhea. [This observation is of great interest to the reviewers because of the possibility that these patients may have had chronic nonspecific colitis as a sequel, a nonspecific infectious sequel, of a specific infection. The suggestion is, of course, not new, but to us it has never been satisfactorily proved or disproved.³⁹⁰ It comes to mind again in connection with Bloom's ³⁹¹ observations on 250 British prisoners of war from prison camps in North Africa. On arrival they were emaciated and apathetic, suffering severely from dysentery, often with incontinence. Various symptoms and signs of vitamin deficiency were noted. *E. histolytica* was demonstrated in the feces, but the patients did not improve clinically under treatment with emetine. The continued dysentery is attributed to mixed infection of the intestine occurring in men weakened by starvation and with little resistance to organisms ordinarily nonpathogenic. The relatively rapid development of vitamin deficiencies and their persistence for months in spite of an adequate intake of vitamins are attributed to malnutrition and poor absorption from an atrophied and ulcerated bowel. In the treatment of these chronic infections diet proved the most important factor. Meat was much more readily assimilated than milk even when the disease was extensive. Milk in large quantities may be definitely harmful. The condition of many of the men apparently had been made worse by indiscriminate dosing with "salts." This is considered a dangerous practice. Sulfaguanidine appeared to be remarkably beneficial.]

Halpert and Ashley ³⁹² add 1 case to the 61 cases of amebic abscess of the brain recorded in the literature.

Emetine has no rival in the treatment of the acute symptoms of intestinal amebiasis and hepatitis even in the presuppurative phase. On the other hand, in 126 patients with chronic amebiasis treated by D'Antoni with diodoquin 92 per cent effectiveness was observed with a single course and 99 per cent effectiveness with two or more courses.³⁹³

(b) Giardiasis: Welch,³⁹⁴ studying 29 cases of giardiasis, found in 73 per cent roentgenographic evidence of changes in the mucosal pattern and in the motor functions of the duodenum, the duodenal cap

390. Miller, F. G.: The Treatment of Dysentery in a Forward Hospital, J. Roy. Army M. Corp. **64**:171-174, 1945.

391. Bloom, H.: Dysentery in British Prisoners of War, Lancet **2**:558-560, 1944.

392. Halpert, B., and Ashley, J. D., Jr.: Amebic Colitis Complicated with Abscess of the Brain, Arch. Path. **38**:112-114 (Aug.) 1944.

393. Arosemena, J.: The Treatment of Amebiasis, New Orleans M. & S. J. **97**:392-400, 1945.

394. Welch, P. B.: Giardiasis with Unusual Findings, Gastroenterology **3**:98-102, 1944.

and the pyloric and prepyloric area. Eosinophilia was present in 75 per cent. Weingarten and Rosenfeld³⁹⁵ report an interesting case in which a 30 year old pregnant woman with vomiting from the fourth to the eighth month of pregnancy was shown by means of biliary drainage to have giardiasis. Under treatment with quinacrine hydrochloride the symptoms disappeared entirely.

(c) Ancylostomiasis and Strongyloidiasis: A study of 71 children with ancylostomiasis revealed marked absence of symptoms referable to hookworm infection, although 1 patient had severe anemia. The degree of infection, i. e., the number of worms present, was not determined. Apparently all the patients had light "worm burdens"; this may account for the low incidence of symptoms. In 4 children with strongyloidiasis, on the other hand, diarrhea and vomiting were present.³⁹⁶

(d) Pinworms: Of 1,871 persons examined for pinworms in a state hospital, 1,100 were infected, the incidence being 72 per cent among the patients with chronic mental diseases and 1 per cent among inebriates. None of the employees was infected. One course of gentian violet medicinal (methylosaniline chloride U. S. P.) provided effective treatment in 91 per cent of the patients. Of 208 reexamined in ten months, 77 (37 per cent) were infected.³⁹⁷

Miller and Einhorn³⁹⁸ in a study of 200 children with pinworms emphasize the diagnostic assistance of the cellophane tip. Treatment was not entirely satisfactory, although gentian violet medicinal appeared to be the best disinfectant tried. However, it can be used only with older children, who, after all, do not constitute a majority of the patients with symptoms. Occasionally, even older children cannot retain the drug because of vomiting. Quassia enemas proved valuable, especially for infants and younger children. This method was troublesome to the mothers, and while it relieved symptoms, it did not always cure the infection. Tetrachloroethylene was of no value.

(e) Schistosomiasis *Mansoni*: In Puerto Rico 10 per cent of healthy male inductees for selective service were shown to have ova of Schis-

395. Weingarten, M., and Rosenfeld, S.: Persistent Vomiting Due to Giardiasis, *Am. J. Digest. Dis.* **12**:54-55, 1945.

396. Miller, J. F.; Einhorn, N. E., and Whittier, L.: Ancylostomiasis and Strongyloidiasis: A Clinical Survey of Seventy-One Cases of Ancylostomiasis and Eleven Cases of Strongyloidiasis in Children, *Am. J. Dis. Child.* **69**:359-365 (June) 1945.

397. Petersen, M. C., and Fahey, J.: Oxyuriasis: Simplified Method of Diagnosis with Glass Slide; Incidence in a Minnesota State Hospital; Result of Treatment with Gentian Violet, *J. Lab. & Clin. Med.* **30**:259-261, 1945.

398. Miller, J. F., and Einhorn, N. H.: Oxyuriasis: A Clinical Survey of Two Hundred Consecutive Cases of Infection with *Enterobius Vermicularis* in Children, *Am. J. Dis. Child.* **68**:376-381 (Dec.) 1944.

tosoma mansoni on routine examination of stools. Proctoscopic examination of 155 infected men revealed ulceration of the rectal mucosa in 60.7 per cent. The mucosa was generally soft, velvety and pale pink, with single or multiple ulcers either pinpoint or linear in shape. The ulcerated area was sharply demarcated from the surrounding normal mucosa, with no zone of inflammation, no crater or ragged edges and no exudate. The ulcer was a noninflammatory break in the continuity, through which oozed a small amount of blood. It was located at the bifurcation of capillaries or was lying directly on them. This relationship of the ulcers to the blood vessels was so constant that a definite relationship could be established. When the ulcers were numerous, they outlined the pattern of the capillaries. The ulcers were below the rectosigmoid fold. Polyps were seen in only 2 instances. Infection with *S. mansoni* indicates schistosomiasis, for there are no healthy carriers.³⁹⁹

Bercovitz, Shwachman and Rodriguez-Molina⁴⁰⁰ analyzed the blood picture in 147 Puerto Rican young men who had no clinical symptoms but in whom infection with *S. mansoni* as well as other intestinal parasites was found. Of 17 infected with *S. mansoni* alone, 5 had leukocytosis and 6 eosinophilia, the highest count of eosinophils being 14 per cent. In 3 no eosinophils were found. In spite of the various parasitic infections present, the blood picture showed a striking resemblance to that in 450 healthy Puerto Rican males free from intestinal and hematogenous parasites.

In 2 cases Di Giacomo and Mayer⁴⁰¹ noted improvement after treatment with fuadin. They emphasize the desirability of obtaining a stool, following the administration of a saline purge, from every person returning to this country.

Colonic Diseases.—(a) Functional Disorders: Jordan⁴⁰² in discussing the problems which the gastroenterologist will face after the war concludes that the chief ones will probably be the functional digestive disorders and peptic ulcer, both of which may have urgent social and economic implications. She emphasizes the common failure to recognize that disordered digestive function readily becomes habitual. Rest is

399. Bercovitz, Z. T.; Rodriguez-Molina, R.; Hargrave, D. W.; Dickie, J. D., and Green, C. E.: Studies on Human *Schistosoma Mansoni* Infections: I. Proctoscopic Picture in Asymptomatic Schistosomiasis *Mansoni* Infections, J. A. M. A. **125**:961-963 (Aug. 5) 1944.

400. Bercovitz, Z. T.; Shwachman, H., and Rodriguez-Molina, R.: The Blood Picture in Asymptomatic *Schistosoma Mansoni* and Other Intestinal Parasitic Infections, Am. J. Trop. Med. **25**:41-45, 1945.

401. Di Giacomo, M. P., and Mayer, R. A.: Schistosomiasis *Mansoni*, J. A. M. A. **125**:904 (July 29) 1944.

402. Jordan, S. M.: Presidential Address: Post-War Rehabilitation of the Digestive Tract, Gastroenterology **3**:73-78, 1944.

the best restorative measure. Peters and Barga⁴⁰³ give an excellent detailed discussion of the syndrome of the irritable bowel.

Kiefer⁴⁰⁴ in analyzing the differential diagnosis of disorders of the small and the large bowel emphasizes the fact that predefecation pain which is relieved by passage of stool or of gas usually is colonic in origin. Pain of the right upper quadrant of the abdomen is common in disorders of the colon; chronic persistent pain of the right lower quadrant of long standing suggests irritation of the cecum rather than appendical inflammation; pain of the lower left quadrant is perhaps more typical of spasticity of the colon, and the classic discomfort of large bowel origin usually is felt across the lower part of the abdomen or even in the back. On the other hand, pain arising from the small bowel has a tendency to be most intense in the upper part of the abdomen or in the periumbilical region.

A physiologic study made by Peterson and Youmans⁴⁰⁵ on the intestinointestinal inhibitory reflex in unanesthetized dogs is of considerable clinical significance. The minimal pressure required to produce a reflex inhibition of intestinal motility falls as the length of the distended jejunum is increased. The intestinal segment then becomes sensitized to redistention, and the same inhibition can be produced with less pressure. The mechanism of action seems to be that of peripheral sensitization occurring at the site of distention. This may represent in part the mechanism or the physiologic basis of irritability of the colon. Of similar physiologic and clinical interest and importance is the observation by Barker⁴⁰⁶ of acute colitis following a soapsuds enema. The colitis was characterized by pain, the passage of serosanguineous fluid and roentgen evidence of extreme irritability and spasm. Jones,⁴⁰⁷ on the other hand, emphasizes the role of emotional tension and presents some interesting cases together with instructive comment. Similarly Alvarez⁴⁰⁸ describes patients without organic disease whose symptoms are aggravated by emotional stress. Reassurance, a low residue diet and sedatives are recommended.

403. Peters, G. A., and Barga, J. A.: The Irritable Bowel Syndrome, *Gastroenterology* **3**:399-402, 1944.

404. Kiefer, E.: Diagnosis of Disorders of the Small and Large Intestine, *New York State J. Med.* **44**:2342-2349, 1944.

405. Peterson, C. G., and Youmans, W. B.: The Intestino-Intestinal Inhibitory Reflex: Threshold Variations, Sensitization and Summation, *Am. J. Physiol.* **143**: 407-412, 1945,

406. Barker, C. S.: Acute Colitis Resulting from Soapsuds Enema, *Canad. M. A. J.* **52**:285, 1945.

407. Jones, C. M.: Functional Gastro-Intestinal Disturbances, *M. Clin. North America* **28**:1154-1163, 1944.

408. Alvarez, W. C.: Distress after Defecation, *Clinics* **3**:577-581, 1944.

(b) Constipation: McGuigan and associates⁴⁰⁹ think that habitual constipation is a common disorder which frequently requires laxative drugs for its treatment. The U. S. P. dose of phenolphthalein (0.06 Gm.) or of aromatic fluid extract of cascara sagrada (2 cc.) is ineffective. Optimal doses are 0.20 Gm. of phenolphthalein and 4 cc. of aromatic fluidextract of cascara sagrada. [The reviewers are of the opinion that the need for this form of treatment is not as common as it is alleged to be. The great majority of persons complaining of constipation are in reality victims of the syndrome of the irritable bowel. However, for some patients the continued use of phenolphthalein and cascara is permissible.]

(c) Megacolon: Grimson and his associates⁴¹⁰ in discussing their experience in 24 cases of Hirschsprung's disease divide the patients into three groups:

Group 1. These patients have uniform involvement of the entire colon terminating in a dilated or easily dilatable rectum. Eight of twelve such patients are now living and are evacuating their colons readily, at an average age of 10 years. One died three years after undergoing sympathectomy, at the age of 24. Of the remaining 3, 1 is having moderately severe trouble at the age of 6, 1 required surgical reduction of a volvulus of the sigmoid at the age of 20 and 1 underwent reduction of a volvulus of the sigmoid at the age of 59, with a recurrence three months later and resection. It appears that protracted medical management of the patients of this group is indicated as long as adequate nutrition can be maintained and persistent abdominal distention avoided. Sympathectomy does not alter significantly the gross pathologic condition, and by interrupting visceral sensory pathways it may permit negligence on the part of the patient with the development of serious impactions. Segmental resection of the colon, as reported in the literature, has been followed frequently by recurrence of impactions proximal to the anastomosis. It would therefore seem that resection of the colon, if indicated for a patient with this condition, should start at the cecum and continue distally through the proximal divisions of the colon to the sigmoid in order that the liquid contents of the ileum may empty into the remaining, and preferably rather short, segment of the involved bowel.

Group 2. These patients have uniform dilatation of the proximal segments of the colon terminating in a normal segment of bowel, usually

409. McGuigan, H. A.; Steigmann, F., and Dyniewicz, J. M.: Evaluation of the Laxative Effect of Some Commonly Used Laxative Substances, with Particular Reference to Dosage, *Am. J. Digest. Dis.* **11**:284-289, 1944.

410. Grimson, K. S.; Vandegrift, H. N., and Dratz, H. M.: Management and Prognosis of Megacolon (Hirschsprung's Disease), *Am. J. Dis. Child.* **68**:102-115 (Aug.) 1944.

in the sigmoid, and a normal rectum. Four of 7 such patients received conventional management and died, 2 at the age of 15 months, 1 at 9 years and 1 at 17 years. One underwent sympathectomy. The remaining 3, with equally severe symptoms and enormous colons, treated unsuccessfully by sympathectomy, underwent, at the ages of 2, 11 and 21, resection of the megacolon with anastomosis between the terminal portion of the ileum and the remaining stump. These 3 are living and well.

Group 3. The patients of this group have enormous enlargement of the sigmoid or of the sigmoid and descending colon, with or without involvement of the proximal portions of the colon and of the rectum. Of 5 such patients, at an average age of 16, 2 were free from symptoms and 3 had moderately severe symptoms. Three of these patients had definitely enlarged rectums and 1 a normal rectum; in 1, during the course of observation, the rectum, which had been normal, became enlarged, with relief of symptoms. Three of the patients independently, by trial and error, determined that laxatives taken once or twice a week produced more effective elimination than laxatives taken daily. The authors conclude that protracted medical management is justified in this group and that in patients with normal segments of the lower sigmoid and rectum these structures may become progressively dilated so that the massive evacuation of impacted material may be accomplished.

Penick⁴¹¹ in the study of 11 cases of congenital megacolon treated by left lumbar sympathectomy reported 7 with highly successful results, 3 with great improvement and 1 with complete failure of treatment. Martin and Ward⁴¹² describe a 22 year old man with megacolon, attributed to a stricture of the sigmoid; the stricture was resected successfully.

(d) Cecitis: Meyer and Disch⁴¹³ describe acute diffuse fatal phlegmonous cecitis.

Rosser⁴¹⁴ reports 2 cases of cecal ulcer clinically indistinguishable from carcinoma. The lesion is usually found on the mesial side of the cecum near the ileocecal valve; it is single, nonspecific and penetrating with a tendency to perforate and to cause extensive scarring. The causation is unknown.

The surgical treatment of benign lesions of the right (or ascending) side of the colon, particularly regional enteritis and granuloma of the cecum, is well presented in another paper.⁴¹⁵

411. Penick, R. M., Jr.: Problems in the Surgical Treatment of Congenital Megacolon, *J. A. M. A.* **128**:423-426 (June 9) 1945.

412. Martin, J. D., Jr., and Ward, C. S.: Megacolon Associated with Volvulus of Transverse Colon, *Am. J. Surg.* **64**:412-416, 1944.

413. Meyer, L. M., and Disch, R.: Acute Phlegmonous Cecitis, *Am. J. Surg.* **68**:398-400, 1945.

414. Rosser, C.: Simple Penetrating Ulcer of the Cecum, *Tr. South S. A* (1943) **55**:89-95, 1944.

(e) Intussusception and Volvulus of Cecum and Colon: Croce and Wiper ⁴¹⁶ describe a cecocolonic intussusception without complete obstruction. No predisposing factor was discovered except the presence of a wide mesentery. Roentgenograms demonstrated the lesion after the use of oral and also rectal administration of barium sulfate.

Levitin and Weyrauch ⁴¹⁷ discuss the differential roentgenologic diagnosis of volvulus and carcinoma of the sigmoid with acute obstruction. The pattern of the shadow of the colon is widest in the cecum in carcinoma, whereas in volvulus the involved loop of sigmoid becomes distended, rises out of the pelvis and lies in the midabdomen. Seven cases of carcinoma and 3 of volvulus are described.

(f) Perforation of Colon: The mortality from traumatic perforation of the colon was reduced from the 50 to 75 per cent range of World War I to 30 per cent in the recent conflict, although the morbidity rate was still high. In 21 cases studied by Colcock ⁴¹⁸ retraction of the colostoma precipitated most of the complications. Traumatic perforations of the colon following intrarectal biopsy, enema and colonic irrigation, respectively, are reported. ⁴¹⁹

(g) Diverticulosis and Diverticulitis of Cecum and Colon: Noon and Schenk ⁴²⁰ describe 3 cases of solitary diverticulum of the cecum with diverticulitis simulating appendicitis. Hendtlass ⁴²¹ reports the perforation of such a diverticulum.

Martin and Adsit ⁴²² in an excellent clinical study of diverticulosis, diverticulitis and carcinoma found that about 5 per cent of patients subjected to roentgen irradiation of the colon for any cause have diverticulosis. In 7,000 consecutive autopsies diverticulosis was present in 3.58 per cent of patients over 40 years. The incidence is 33 per cent higher in females than in males. Diverticulitis developed in 12 to 15

415. Rosser, C.: Benign Surgical Lesions of the Right Colon, *J. A. M. A.* **127**:568-571 (March 10) 1945.

416. Croce, E. J., and Wiper, T. B.: Cecocolic Intussusception in the Adult: Case Report, *Am. J. Surg.* **66**:389-392, 1944.

417. Levitin, J., and Weyrauch, H. B.: Acute Obstruction of the Colon: Differential Diagnosis Between Volvulus and Cancer of the Sigmoid Colon by Preliminary Roentgenogram, *Am. J. Roentgenol.* **53**:132-141, 1945.

418. Colcock, B. P.: Postoperative Problems Following Perforation of Colon, *Army M. Bull.* 1944, no. 80, pp. 106-108.

419. Kaufman, L. R.; Serpico, S., and Mosig, H. J.: Perforation of the Rectosigmoid, *Surgery* **17**:337-342, 1945.

420. Noon, Z. B., and Schenk, H. L.: Solitary Diverticulitis of the Cecum, *Am. J. Surg.* **68**:364-368, 1945.

421. Hendtlass, R. F.: Perforated Solitary Diverticulum of Caecum, *Brit. M. J.* **2**:309-310, 1944.

422. Martin, K. A., and Adsit, C. G.: Diverticulosis and Diverticulitis: A Clinical Study of the Complications, *M. Clin. North America* **29**:639-654, 1945.

per cent of patients with diverticulosis. At New York Hospital, in 177,718 admissions from 1933 to 1944, 201 cases of diverticulitis were encountered; 28 were of Meckel's type. Operation for some complication was performed in 51 cases, with 12 deaths (23.5 per cent). Carcinoma was observed in association with diverticulitis four times (7.8 per cent) and with diverticulosis thirteen times. Allen⁴²³ states that 22 per cent of patients with diverticulitis come to operation because of acute perforation, obstruction of the sigmoid, fistula, localized abscess or inability to rule out carcinoma. A history of bleeding was obtained from 25 per cent. Lesions located in the sigmoid are the most favorable for surgical intervention. The trend is toward more radical surgical intervention with the first operation, i. e., resection of the involved segment at the time of exploration, rather than the two stage colostomy followed by resection.⁴²⁴ Jones⁴²⁵ likewise discusses the surgical treatment of inflammatory lesions of the colon.

Bonorino Udaondo⁴²⁶ gives an excellent review of inflammation of the sigmoid part of the colon.

(h) Ulcerative Colitis: The increasing incidence of inflammatory disease of the colon is illustrated by the fact that 650 patients with colitis were seen at the Mayo Clinic in 1943; 520 with ulcerative colitis, 43 with intestinal tuberculosis; 82 with amebiasis and 5 with lymphopathia venereum.⁴²⁷ Winkelstein⁴²⁸ summarizes a discussion by stating that the disease is common, crippling and baffling in its nature, that it has a high mortality, that medical therapy has advanced chiefly in the use of transfusion and antitoxic B. coli serum and that surgical therapy is still on trial. All in all, ulcerative colitis remains definitely "colitis gravis."

Present knowledge of regional segmental ulcerative colitis derives largely from the excellent studies made by Bargen and his associates.⁴²⁹ A recent report indicates that this condition was diagnosed in 68 patients—4 per cent of the total number with ulcerative colitis. With regard

423. Allen, A. W.: Abdominal Surgery, *New England J. Med.* **232**:165-173, 1945.

424. Rosser, C.: Diverticulitis: Indications for Resection, *South. M. J.* **38**: 161-166, 1945.

425. Jones, T. E.: Inflammatory Lesions of the Colon, *J. A. M. A.* **126**: 1013-1015 (Dec. 16) 1944.

426. Bonorino Udaondo, C.: Las sigmoiditis infiltrantes y su tratamiento, *Rev. de gastro-enterol. de México* **9**:137-157, 1944.

427. Bargen, J. A.: Annual Report on Intestinal Diseases for 1943, *Proc. Staff Meet., Mayo Clin.* **19**:602-605, 1944.

428. Winkelstein, A.: Ulcerative Colitis, *J. Mt. Sinai Hosp.* **11**:159-163, 1945.

429. de Castro Barbosa, J.; Bargen, J. A., and Dixon, C. F.: Regional Segmental Colitis, *Proc. Staff Meet., Mayo Clin.* **20**:134-143, 1945.

to therapy the conclusion is reached that all such patients should receive an adequate medical regimen, that resection is probably the treatment of choice, that the time of such resection must be carefully determined by the clinician and the surgeon working together, that adequate pre-operative management is of the greatest importance and that short circuiting operations do not yield final good results.

The similarity between the red, turgescient, friable mucosa of the bowel in ulcerative colitis and the skin around the site of an ileostomy or a duodenal fistula resulting from enzymatic digestion suggested to Portis, Block and Necheles⁴³⁰ that enzymatic factors might be operative in ulcerative colitis. The rectal discharge of such patients was found to contain moderate amounts of trypsin. Perfusion of the colon of a dog with trypsin solution led to irritation, hemorrhage and a large increase of mucus. Sodium lauryl sulfate, Abbott (sodium-lauryl-myristal-cetyl and stearyl sulfates, containing 50 per cent sodium sulfate) promoted the healing of cutaneous wounds in animals and in man, but the oral ingestion of detergents did not regularly reduce the enzyme content in the ileal discharge of 9 patients who had undergone ileostomy. [The reviewers find themselves unable to accept this interesting hypothesis until more satisfactory evidence is presented.]

Martin⁴³¹ reports extensive thrombosis of the abdominal aorta, the right and left common iliac arteries and the left renal arteries, and infarcts of the kidneys, the spleen, the pancreas and the myocardium arising from mural endocarditis complicating extensive chronic ulcerative colitis.

Bargen and Sauer⁴³² in an excellent article on ulcerative colitis and carcinoma refer to Bargen's paper of 1929 reporting a 10 per cent incidence of polyposis in 693 cases of chronic ulcerative colitis and an incidence of carcinoma of 2.5 per cent. The present paper is an analysis of 30 additional cases, bringing the total number of cases of chronic ulcerative colitis complicated by carcinoma at the Mayo Clinic to 54. Only 3 of the patients were over 35 years of age at the time of the onset of the colitis. The shortest interval between the onset of the disease and the appearance of symptoms suggesting carcinoma was four years; the longest, forty-two years. In 9 of the 30 cases multiple carcinoma was found, most of the lesions being of the higher grades of malignancy. Sipman⁴³³ reports ulcerative colitis with polyposis com-

430. Portis, S. A.; Block, C. L., and Necheles, H.: Studies on Ulcerative Colitis and on Some Biological Effects of Detergents, *Gastroenterology* **3**:106-113, 1944.

431. Martin, M. E.: Arterial Thrombosis Associated with Chronic Ulcerative Colitis, *Am. J. Digest. Dis.* **12**:85-88, 1945.

432. Bargen, J. A., and Sauer, W. G.: The Association of Chronic Ulcerative Colitis and Carcinoma, *Clinics* **3**:516-534, 1944.

433. Sipman, H.: A Malignant Tumor Developing in a Defunctioned Colon of Twenty Years Standing, *Clinics* **3**:1059-1061, 1944.

pletely asymptomatic for eighteen years, following permanent cecostomy. An anaplastic carcinoma of the rectum was found on proctoscopic examination and later resected.

Bargen⁴³⁴ reviews the therapy of ulcerative colitis and reports that the effect of phthalylsulfathiazole was good in 26, fair in 1, slight in 1 and not apparent in 9. The toxicity seems less than that of many drugs commonly used in intestinal diseases.⁴³⁵ Poth and Ross⁴³⁶ found that phthalylsulfathiazole is twice as effective as succinylsulfathiazole in altering the coliform flora of the bowel in man. The drug has low toxicity and is well tolerated by patients with ulcerative colitis. Pollard⁴³⁷ found no "significant amount of sterilization of the bowel" but did think that succinylsulfathiazole produced "a definite and at times dramatic clinical response in three fourths of the thirty-six patients." Bargen⁴³⁸ considers succinylsulfathiazole and azosulfamide most effective in nonspecific ulcerative colitis, sulfathiazole of value in venereal lymphogranuloma and succinylsulfathiazole most promising in regional colitis. All have been used with indifferent success in regional enteritis. In summary, the results are relatively satisfactory in a few conditions and disappointing in others. Collins⁴³⁹ concludes that "sulfonamides have a place in the treatment of ulcerative colitis but we do not know which patient will be benefited." Azosulfamide or sulfadiazine or the two combined are preferred in cases of toxic disease; succinylsulfathiazole, in early stages of nontoxic disease.

In 145 cases of idiopathic ulcerative colitis 11 acute perforations occurred, followed by peritonitis and rapid death. The incidence of perforation was 7 per cent; the mortality, 100 per cent. Seven were primary in the colon and 4 in the ileum, following operative procedures.⁴⁴⁰

Garlock⁴⁴¹ considers surgical treatment to be in order for ulcerative colitis in the presence of uncontrollable hemorrhage, profound toxemia

434. Bargen, J. A.: The Medical Management of Ulcerative Colitis, *J. A. M. A.* **126**:1009-1013 (Dec. 16) 1944.

435. Bargen, J. A.: Sulfathalidine in Intestinal Diseases, *Proc. Staff Meet. Mayo Clin.* **20**:85-87, 1945.

436. Poth, E., and Ross, C. A.: The Clinical Use of Phthalylsulfathiazole, *J. Lab. & Clin. Med.* **29**:785-808, 1944.

437. Pollard, H. M.: III. The Clinical Use of Succinyl Sulfathiazole in Chronic Ulcerative Colitis, *Gastroenterology* **4**:4-8, 1945.

438. Bargen, J. A.: The Sulfonamide Compounds in Treatment of Diseases of the Intestine, *M. Clin. North America* **28**:811-824, 1944.

439. Collins, E. N.: IV. Late Results in Ulcerative Colitis, *Gastroenterology* **4**:8-10, 1945.

440. Jankelson, I. R.; McClure, C. W., and Sweetsir, F.: Idiopathic Ulcerative Colitis: Perforation of the Bowel, *Rev. Gastroenterol.* **12**:31-37, 1945.

441. Garlock, J. H.: Further Experiences with the Surgical Treatment of Intractable Ulcerative Colitis, *New York State J. Med.* **45**:1309-1312, 1945.

not responding to medical treatment, impending perforation, polypoid degeneration, extensive scarring and retrovaginal fistula. Ileostomy is indicated in all, followed by graded resection of the colon in the last three groups.

Ileostomy was the primary operation in 38 patients, with 6 deaths, a mortality of 15.7 per cent. Five of the remaining 32 were subjected to subtotal colectomy followed by abdominoperineal resection of the rectum, with no deaths. In 21 of the 38 patients with ileostomy subtotal colectomy was carried out without removal of the rectum. There were 4 deaths, a mortality of 19.9 per cent, peritonitis being the most common cause of death. An ileorectal anastomosis was made in 6 of the 17 remaining patients. Three are alive and are progressing favorably after two, three and five years, respectively; 3 died. Of 6 undergoing primary transverse colostomy for left-sided disease, colectomy on the left side and abdominoperineal resection were carried out in 5, and colectomy on the left alone only in 1, with 1 death. In 13 of another group with primary ileoproctostomy or ileosigmoidostomy and exclusion of the diseased bowel, followed by subtotal colectomy in one stage, there were no postoperative deaths; 11 of this group are progressing favorably, with follow-up studies of nine months to seven years. Of 10 patients with segmental colitis, ileosigmoidostomy was done in 7, with 2 postoperative deaths. The 5 survivors are doing well. In the series of 146 patients who underwent major operations there were 8 in whom acute intestinal obstruction occurred at varying times after they were discharged from the hospital, with death resulting from the obstruction in 5.

During an eight year period Cave⁴⁴² operated on 92 persons, 18 of whom died, an operative mortality of 19.5 per cent. During the first two years emergency operations were performed on 15 patients whose disease was in the acute fulminating stage, 8 of whom died, an operative mortality of 53 per cent. In an elective group of 50 patients treated by ileostomy there were 4 deaths, an operative mortality of 8 per cent. The principal indication for emergency operation is perforation. Cave advocates ileostomy followed in six months by subtotal colectomy for patients not responding to medical management.

Of 82 patients with ulcerative colitis, 57 were treated conservatively, with 16 deaths (28 per cent), and 25 surgically with 3 deaths (12 per cent). Dennis⁴⁴³ emphasizes the psychiatric aspects of the disease and suggests that early ileostomy may offer the most effective therapy.

442. Cave, H. W.: *Surgical Experiences with Ulcerative Colitis*, S. Clin. North America **25**:301-306, 1945.

443. Dennis, C.: *Surgery in Relation to Chronic Non-Specific Ulcerative Colitis: Experience at the University of Minnesota Hospitals*, Minnesota Med. **28**:228-234, 1945.

The second edition of "Cancer of the Colon and Rectum" is another standard work to be recommended but not reviewed here.⁴⁴⁴

(i) Benign and Malignant Tumors: Browne and McHardy⁴⁴⁵ discuss submucosal lipoma of the colon, 130 cases of which have been collected from the literature.

Atwater and Bargaen⁴⁴⁶ in an excellent paper trace the pathogenesis of intestinal polyps from the earliest epithelial change to frank carcinoma. In 241 consecutive necropsies polyps were found in 166, an incidence of 69 per cent. In accord with the concept of the malignant degeneration of benign polyps is the report by Berson and Berger⁴⁴⁷ of 13 cases each with two independent cancers and 3 cases each with three malignant growths. The frequency of multiple cancer was found to be 4.6 per cent. In a survey of the literature, beginning with 1932, they collected 66 cases with two and 6 cases with three cancers. Bacon and Gass⁴⁴⁸ describe 5 cases of multiple primary cancer of the rectum and sigmoid colon. An average of 8.8 cases of this type are reported in the literature each year. Murray⁴⁴⁹ reports the coincidence of a mother and her son coming to his office on the same day, each with multiple adenoma of the sigmoid undergoing malignant change.

Oppenheimer⁴⁵⁰ recommends the use of small amounts of opaque material (30 to 60 cc.) for the diagnosis of early small neoplastic lesions of the rectum, and Whitehead⁴⁵¹ advocates proctoscopy as a routine measure to precede the administration of the barium sulfate enema. Christianson⁴⁵² calls attention to certain difficulties in the visualization of rectal lesions on proctoscopy, particularly in that of prolapsing pedunculated tumor of the sigmoid, and emphasizes the importance of the routine proctoscopic examination. The technical difficulties of

444. Rankin, F. W., and Graham, A. S.: *Cancer of the Colon and Rectum*, Springfield, Ill., Charles C Thomas, Publisher, 1939.

445. Browne, D. C., and McHardy, G.: Submucosal Colon Lipomas: Case Report; Mucocoele of Appendix as Complication, *Clinics* 3:622-629, 1944.

446. Atwater, J. S., and Bargaen, J. A.: The Pathogenesis of Intestinal Polyps, *Gastroenterology* 4:395-408, 1945.

447. Berson, H. L., and Berger, L.: Multiple Carcinomas of the Large Intestine, *Surg., Gynec. & Obst.* 80:75-84, 1945.

448. Bacon, H. E., and Gass, O. C.: Multiple Primary Malignant Neoplasms of the Rectum and Sigmoid Colon: Report of Five Additional Cases, *Am. J. Surg.* 68:240-249, 1945.

449. Murray, F. H.: Multiple Adenomata Undergoing Malignant Changes in Mother and Son, *Clinics* 3:1035-1038, 1944.

450. Oppenheimer, A.: Roentgen Diagnosis of Incipient Cancer of the Rectum, *Am. J. Roentgenol.* 52:637-646, 1944.

451. Whitehead, L. J.: Roentgenological Manifestation of Malignancy of the Colon, *South. M. J.* 38:85-89, 1945.

452. Christianson, H. W.: Prolapsing Tumors of the Rectum and Sigmoid, *Clinics* 3:1023-1034, 1944.

demonstrating polyposis of the colon are illustrated in 2 brief case reports.⁴⁵³ Womack⁴⁵⁴ stresses the fact that the gross appearance of rectal adenoma may give a true indication of the degree of malignancy, whereas the histologic study of the portion removed for biopsy may fail to do so. The importance of securing for biopsy a specimen including a portion of the base of the lesions is emphasized. Complete extirpation of all benign lesions is advised.

In 1942 the population of Greater New York was 7,300,000. During that year 1,962 persons died of cancer of the stomach, 1,616 of cancer of the colon and 911 of cancer of the rectum. The combined death rate for cancer of the colon and the rectum was 2,527, or 600 more than the rate for cancer of the stomach.⁴⁵⁵

The location of 778 carcinomas of the large intestine operated on at the Mayo Clinic in 1943 was as follows: rectum, 32 per cent; sigmoid, 28 per cent; rectosigmoid, 12.5 per cent; descending colon, 7.4 per cent; cecum, 5.5 per cent; transverse colon, 4.1 per cent; ascending colon, 3.6 per cent; splenic flexure, 3.2 per cent; hepatic flexure, 2.7 per cent; anus, 0.4 per cent.⁴⁵⁶

In an analysis of data on acute obstruction due to carcinoma of the colon, Gruenfeld⁴⁵⁷ points out that about 20 to 30 per cent of patients with such involvement of the colon (rectum and rectosigmoid excluded) suffer an attack of complete (acute) obstruction. Complete obstruction with meteorism endangers the viability of the cecum. Decompression by colostomy is advised, followed by resection of the tumor-bearing area. Finn and Lord⁴⁵⁸ report the successful removal without miscarriage of a carcinoma of the colon which produced acute intestinal obstruction during pregnancy.

A carcinoma of the sigmoid with an intercolic fistula extending to the transverse colon and an external fistula with abscess formation, requiring resection of the transverse colon, splenic flexure, descending colon and sigmoid, is reported by Gratiot and Nunes.⁴⁵⁹

453. Schutte, A. G.: Difficulties in Roentgenographic Diagnosis of Polyposis of the Colon, *Clinics* **3**:1039-1044, 1944.

454. Womack, N.: Adenoma of the Rectum, *S. Clin. North America* **24**: 1143-1150, 1944.

455. Heyd, G.: The Curability of Cancer of the Large Bowel, *Rev. Gastroenterol.* **12**:23-30, 1945.

456. Bargaen, J. A.: Annual Report on Intestinal Diseases for 1943, *Proc. Staff Meet., Mayo Clin.* **19**:602-605, 1944.

457. Gruenfeld, G. E.: Acutely Obstructing Carcinoma of the Colon, *S. Clin. North America* **24**:1126-1142, 1944.

458. Finn, W. F., and Lord, J. W., Jr.: Carcinoma of the Colon Producing Acute Intestinal Obstruction During Pregnancy, *Surg., Gynec. & Obst.* **80**:545-548, 1945.

459. Gratiot, J. H., and Nunes, A. J.: Combined Intercolic and External Fistula Caused by Carcinoma of the Sigmoid, *Am. J. Surg.* **66**:265-268, 1944.

In a statistical discussion Pemberton and his associates⁴⁶⁰ point out that the mortality from operations on the large intestine was 13.1 per cent in 1933, while it was 3.3 per cent in 1943. The chief cause of death continues to be infections, 50 per cent of which are peritoneal. Collier and Vaughan⁴⁶¹ report 173 patients with carcinoma of the colon treated by operation. In 60 of the lesions of the ascending colon, the mortality was 6.6 per cent; in 21 of the transverse colon, 23.8 per cent; in 9 of the splenic flexure, 11.11 per cent; in 13 of the descending colon, no mortality, and in 70 of the sigmoid, 4.2 per cent mortality. Eighty-three per cent of lesions were considered resectable. The mortality from resection was 4.1 per cent and the over-all mortality 7.5 per cent. In a group of 110 patients with colonic carcinoma (exclusive of the rectum and the sigmoid), 85 resections (77.3 per cent) were performed. The high rate of resectability is attributed to the increasing use of primary closed resection in the descending (left) colon. In the hands of White and Amendola⁴⁶² the mortality rate from closed resection was one half that from the Mikulicz type of resection. Babcock and Bacon⁴⁶³, in an analysis of 712 operations conclude that the tendency is toward a wider use of end to end resection, the preservation of the uninvolved anus and the elimination of the Mikulicz operation except when serious peritoneal contamination renders a rapid termination of the intra-abdominal procedure desirable.

Pfeiffer and Levering⁴⁶⁴ in analyzing 179 cases found that in 108 the tumor was located in the rectum or the sigmoid and that in almost 50 per cent of this group it could be found by digital rectal examination. One hundred and sixty-four patients were operated on (91.6 per cent operability), and the growth was resected in 106 of these (64.6 per cent). The postoperative mortality was 20.1 per cent, although in favorable cases it was only 5.5 per cent. In 256 cases studied by Bacon and his associates⁴⁶⁵ the cancer was resectable in 208 (81.2 per cent).

460. Pemberton, J. deJ.; Dixon, C. F.; Waugh, J. M., and Black, B. M.: Annual Report of Surgery of the Large Intestine for 1943, Proc. Staff Meet., Mayo Clin. **19**:605-612, 1944.

461. Collier, F. A., and Vaughan, H. H.: Treatment of Carcinoma of the Colon, Ann. Surg. **121**:395-411, 1945.

462. White, W. C., and Amendola, F. H.: The Advantages and Disadvantages of Closed Resection of the Colon, Ann. Surg. **120**:572-581, 1944.

463. Babcock, W. W., and Bacon, H. E.: Complications in the Surgical Treatment of Carcinoma of the Large Bowel, J. A. M. A. **128**:73-77 (May 12) 1945.

464. Pfeiffer, D. B., and Levering, J. W.: Carcinoma of the Large Bowel: A Review of Cases Treated by the Pfeiffer Surgical Clinic over a Five-Year Period—1939 to 1943 Inclusive, Clinics **4**:27-35, 1945.

465. Bacon, H. E.; Gass, O. C., and Todhunter, W. D.: The Present Status of the Surgical Treatment of Cancer of the Rectum and Pelvic Colon, Clinics **3**:982-986, 1944.

The operative mortality from resection was 7.6 per cent. Metastases were found in the liver in 8.4 per cent and in regional lymph nodes in 37.2 per cent. Cole ⁴⁶⁶ reports 50 consecutive cases of carcinoma of the colon. Partial or complete obstruction occurred in 60 per cent of the cases of tumor of the descending colon; the operative mortality was 32 per cent. Obstruction occurred in 16.6 per cent of those involving the ascending colon, with an operative mortality of 10 per cent.

Poth ⁴⁶⁷ discusses the importance of the preoperative administration of sulfonamide drugs. The results obtained when succinylsulfathiazole and when phthalylsulfathiazole was used are compared. The former gave a better mechanical cleansing, due to the more fluid feces. Ten years ago the mortality from primary surgical treatment of the colon was 10 per cent; today with good preoperative and postoperative care, including the administration of sulfonamide drugs, the mortality has been reduced to 2 per cent. A coliform count of 1,000 organisms per gram of feces is considered adequate. The usual dosage of succinylsulfathiazole was 0.02 Gm. per pound of body weight every four hours or 3.0 Gm. every four hours for an average-sized man of 150 pounds (68 Kg.) (approximately 0.25 Gm. per kilogram of body weight). The corresponding dose of sulfathalidine is 1.5 Gm. every four hours.

Dixon and Benson ⁴⁶⁸ report that in cases of closure of a colonic stoma infection of the operative wound occurred in 84 per cent and a fecal fistula developed in 30 per cent of a series of 102 cases in which no sulfonamide compound was employed, whereas infection of the wound occurred in only 13 per cent and a fecal fistula in only 2 per cent of 102 cases in which a combination of succinylsulfathiazole and sulfathiazole was administered. In Behrend's ⁴⁶⁹ hands the preoperative use of succinylsulfathiazole has reduced the hospital stay of patients undergoing operation on the colon from an average of 65.1 days to 27.4 days by allowing resection with end to end anastomosis to be substituted for the Mikulicz operation.

Emmett and Cristol ⁴⁷⁰ report 33 cases in which resection of the rectum or the sigmoid complicated by obstruction of the vesical neck

466. Cole, W. H.: Carcinoma of the Colon, *Rocky Mountain M. J.* **42**:169-178, 1945.

467. Poth, E. J.: Succinylsulfathiazole and Phthalylsulfathiazole in Surgery of the Colon, *Surgery* **17**:773-780, 1945.

468. Dixon, C. F., and Benson, R. E.: Closure of Colonic Stoma: Improved Results with Combined Succinylsulfathiazole and Sulfathiazole Therapy, *Ann. Surg.* **120**:562-571, 1944; *Tr. Am. Surg. A.* **62**:562-571, 1944.

469. Behrend, M.: Colon Surgery and the Sulfonamide Drugs with Especial Reference to the Elimination of the Mikulicz Operation, *J. A. M. A.* **128**:9-12 (May 5) 1945.

470. Emmett, J. L., and Cristol, D. S.: Urinary Retention Following Surgical Operation on the Rectum and Sigmoid, *J. A. M. A.* **126**:1077-1079 (Dec. 23) 1944.

did not respond to the usual medical measures. Transurethral resection of the prostate resulted in excellent results in 30, poor in 2 and fair in 1.

Tilton⁴⁷¹ describes a 73 year old woman with an inoperable tumor, which was found to be a lymphosarcoma.

Squamous cell carcinomas comprise about 5 per cent of the malignant tumors of the anus and the rectum; the remainder are almost all adenocarcinomas. Of 40 squamous cell carcinomas, 34 occurred in females and 6 in males. Thirty-nine of these tumors could be palpated on digital examination. Anal fissure is often confused with squamous cell carcinoma. Inguinal metastases occur not infrequently. The tumor grows slowly and can be treated either by surgical resection or irradiation. Seven of 40 patients survived five years or more clinically free of cancer.⁴⁷²

Bacon and Pena⁴⁷³ present 2 cases of malignant melanoma of the anorectum, emphasizing the extreme malignancy of the tumor.

Yaker⁴⁷⁴ reports a carcinoid of the rectum and discusses the difficulties of pathologic diagnosis. The rarity of the lesion is shown by the fact that Stout found only 12 cases reported in the literature.

Jackman and Buie⁴⁷⁵ excised submucosal rectal nodules of varying size, which were found just proximal to the dentate margin; 59.5 per cent were chemical in origin, following treatment by injection; 4.2 per cent were carcinoids; 4.2 per cent, lymphosarcoma; 10 per cent, benign tumors (fibroma, lipoma, leiomyoma), and 21.1 per cent were inflammatory.

(j) Syphilis and Lymphopathia Venereum: An unusual case of syphilis with rectal stricture is reported by Melamed and Feld.⁴⁷⁶ The Frei test was repeatedly negative, and the lesion improved remarkably under antisyphilitic therapy.

Woods and Hanlon⁴⁷⁷ analyze data on 192 inflammatory strictures of the rectum. In 86 per cent of 105 cases in which tests with lympho-

471. Tilton, B. T.: Carcinoma and Lymphosarcoma of the Colon: A Case of Lymphosarcoma of the Descending Colon, *Am. J. Surg.* **66**:300-308, 1944.

472. Keyes, E. L.: Squamous Cell Carcinoma of the Anus and Rectum, *S. Clin. North America* **24**:1151-1161, 1944.

473. Bacon, H. E., and Pena, E.: Malignant Melanoma of the Anorectum: Report of Two Cases, *Clinics* **3**:457-464, 1944.

474. Yaker, D. N.: Carcinoid of the Rectum, *Clinics* **37**:1055-1058, 1944.

475. Jackman, R. J., and Buie, L. A.: Submucosal Nodules of the Rectum, *S. Clin. North America* **24**:903-909, 1944.

476. Melamed, A., and Feld, S. M.: Luetic Rectal Stricture, *Am. J. Digest. Dis.* **12**:203-206, 1945.

477. Woods, F. M., and Hanlon, C. R.: Inflammatory Strictures of the Rectum: An Analysis of One Hundred and Ninety-Two Cases, Including Thirty-Five Treated by Rectosigmoid Resection, *Ann. Surg.* **120**:598-606, 1944.

pathia venereum antigen were made positive reactions were obtained. Various methods of treatment were used, with inconclusive results. Thirty-five patients underwent resection of the rectosigmoid, with no deaths. David, in the discussion, mentions marked improvement or cure in many such patients from the use of the sulfonamide drugs, but concludes nevertheless that resection is indicated for dense fibrous strictures.

(*k*) Irradiation Injury: McIntosh and Hutton⁴⁷⁸ report 44 cases of temporary or permanent stricture of the bowel following irradiation of carcinoma of the cervix. In 33 the process was confined to the pelvic colon and the rectum. Severe and extensive irradiation injury of the bowel may undergo healing with little or no functional impairment in spite of marked anatomic narrowing. Careful medical treatment, consisting of a bland low residue diet and the use of antispasmodic drugs, is of value. Black and Waugh⁴⁷⁹ report segmental resection of such a stricture.

(*l*) Foreign Bodies: Akcakoyunlu⁴⁸⁰ reports that a 40 year old woman spontaneously passed through the rectum a Kocher forceps left within the peritoneal cavity at a gynecologic operation fourteen months earlier.

(*m*) Congenital Anomalies: Lee⁴⁸¹ presents an analysis of 16 cases to emphasize the high frequency with which fistula between the rectum and the genitourinary tract is associated with deformity of the lower part of the rectum.

(*n*) Pruritus Ani: McCutchan⁴⁸² concludes that pruritus ani is a symptom complex and not a disease.

478. McIntosh, H. C., and Hutton, J. E.: Clinical and Roentgen Aspects of Irradiation Stricture of the Rectum and Sigmoid: Its Course and Treatment, *Am. J. Roentgenol.* **52**:647-662, 1944.

479. Black, W. A., and Waugh, J. M.: Successful Resection for Stricture of the Recto-Sigmoid and Repair of Rectovaginal Fistula Following Radium Therapy for Carcinoma of Cervix: Report of Case, *Proc. Staff Meet., Mayo Clin.* **20**: 87-89, 1945.

480. Akcakoyunlu, I.: Spontaneous Expulsion Through the Rectum of a Kocher Forceps Left in the Abdomen Fourteen Months, *Brit. M. J.* **2**:182, 1944.

481. Lee, M. J., Jr.: Congenital Anomalies of the Lower Part of the Rectum: Analysis of Sixteen Cases, *Am. J. Dis. Child.* **68**:182-189 (Sept.) 1944.

482. McCutchan, G. R.: Pruritus Ani, *Am. J. Digest. Dis.* **12**:171-174, 1945.

News and Comment

GENERAL NEWS

Twenty-Fifth Anniversary of the Discovery of Insulin.—The twenty-fifth anniversary of the discovery of insulin will be observed with a program in Convocation Hall, at the University of Toronto, on September 16. Many internationally known figures in the field of medicine will be present to honor the occasion. Among them will be R. D. Lawrence, physician in charge, Diabetic Clinic, King's College Hospital, London, England; H. C. Hagedorn, Gentofte, Denmark; Bernardo A. Houssay, Research Institute of Experimental Biology and Medicine, Buenos Aires, Argentina, and Elliott P. Joslin, Harvard Medical School, Boston. This observation will be followed by the regular annual meeting of the American Diabetes Association.

On September 23 Eli Lilly and Company will sponsor an International Diabetes Clinic to be held at the Indiana University Medical Center in Herty Hall of the State Board of Health Building, Indianapolis. International importance will be given to this meeting by the presence of Professor Charles H. Best, Toronto, Canada, co-discoverer with Banting of insulin, Professor Houssay, Dr. Lawrence and Dr. Hagedorn. They will discuss various phases of diabetic care.

Book Reviews

Experimental Studies on the Vasomotor Innervation of the Retinal Arteries (Tr. by Robert Fraser). By Kaj Robert Porsaa. Price, 10 Danish kroner. Pp. 201, with 55 illustrations. Copenhagen: Einar Munksgaard, 1941.

Much interest and some controversy have arisen in the past over the question as to whether or not the retinal arteries and those of the brain behave physiologically alike in all respects. The author by carefully controlled and ingenious experiments has probably demonstrated that they do.

The experimental work, that is carefully detailed, had for its objective the elucidation of the vasomotor innervation of the retinal arteries and the relation of this innervation to the circulation in the other parts of the organism, particularly in the brain. It showed, among other things, that the retinal arteries are not directly controlled by the vasosensory nerves and are not subject to the regulation of the universal circulation. In fact, the retinal arteries, in the experiments, behaved precisely as do the cerebral arterioles of the same order of magnitude.

One of the most interesting chapters is that having to do with the relation of the retinal arteries to experimentally produced variations in blood pressure by compression of the abdominal aorta, drugs, faradic stimulation of the depressor nerve, diminution of the intravascular blood volume and inhibition of the heart action.

This work, therefore, is not without some clinical importance to the internist, physiologist, neurologist and ophthalmologist. It will bear their careful attention.

The Cookery Book for Diabetics. Compiled by The Diabetic Association, 9 Manchester Square, London, W. 1. With a foreword by Prof. V. H. Mott-ram. Price, 4s. Pp. 82, with illustrations. London, England: H. K. Lewis & Co., 1945.

"First Lessons in Food Values" and "Hints for Diabetic Cookery," as presented in the first few pages of this book, are well worth reading for the diabetic patient, the dietitian and the physician. Here is a clear and simple explanation of what can be a difficult subject for the average patient. The data on rationed foods and many of the recipes, being typically English, will not interest the American diabetic patient. However, the recipes for salads and for desserts might be helpful. They are arranged as to carbohydrate value; amounts vary from 0 to 20 Gm. of carbohydrate per serving. In order to use these recipes to his advantage the patient with diabetes would have to be familiar with making substitutions.

Cornell Conferences on Therapy. By Harry Gold, M.D. Volume 1. Price, \$3.25. Pp. 322. New York: The Macmillan Company, 1946.

A great many doctors have read with interest and profit the "Cornell Conferences on Therapy" as they appeared in the *New York State Journal of Medicine*. It is therefore a satisfaction to have some of these authoritative discussions available in book form.

Among the fifteen topics selected for volume 1 is a variety of subjects, including five on various aspects of heart disease. Aside from the "regulars"—Dr. Gold, Dr. Cattell and others—some guest specialist usually participates and the presentation of part of the discussion in the form of a dialogue adds vivacity and "punch" to what is said.

The book makes for good reading and will be most useful as a reference. One wonders whether an index would not have been worth while.

HEMOLYTIC STREPTOCOCCIC AND NONSTREPTOCOCCIC DISEASES OF THE RESPIRATORY TRACT

A Comparative Clinical Study

LOWELL A. RANTZ, M.D.
SAN FRANCISCO

PAUL J. BOISVERT, M.D.
NEW HAVEN, CONN.

AND

WESLEY W. SPINK, M.D.
MINNEAPOLIS

GREAT interest has been aroused in hemolytic streptococcic infection of the respiratory tract during recent years. This has been the result of the demonstration that such infection frequently initiates a complex nonsuppurative process, of which rheumatic fever is the most important and dramatic manifestation. A recent critical study¹ showed that this disease was invariably preceded by a hemolytic streptococcic infection. In spite of this fact, definitive clinical studies of the nature of streptococcic infection of the respiratory tract are almost nonexistent. The Dicks² and Dochez³ established the fact that scarlet fever is caused by hemolytic streptococci and showed that experimental infection in human beings was not always associated with rash formation. An immunologic explanation of this phenomenon

The laboratories of the Department of Medicine, Stanford University School of Medicine, San Francisco, were made available to the Commission for certain purposes.

Col. T. E. Harwood Jr., Major James Blanton and Capt. Howard Coggeshall assisted in the preparation of this paper. Elizabeth Randall, Viola Ferris, Loraine Kerr and Helen Rantz were responsible for the technical and secretarial work.

This investigation was carried out during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

1. Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: The Etiology and Pathogenesis of Rheumatic Fever, *Arch. Int. Med.* **76**:131 (Sept.) 1945.

2. Dick, G. F., and Dick, G. H.: Experimental Scarlet Fever, *J. A. M. A.* **81**:1166 (Oct. 6) 1923.

3. Dochez, A. R., and Sherman, L.: Significance of *Streptococcus Hemolyticus* in Scarlet Fever: Preparation of a Specific Anti-Scarlatinal Serum by Immunization of Horse to *Streptococcus Hemolyticus-Scarlatinae*, *J. A. M. A.* **82**:542 (Feb. 16) 1924.

was offered. Adequate monographs describing the natural history of scarlet fever are available but deal largely with the disease as observed in children.⁴

The splendid work of Lancefield⁵ has demonstrated that nearly all hemolytic streptococcic infections of the respiratory tract in human beings are caused by a single serologic group of the hemolytic streptococci, designated by the letter "A," and that this group may be subdivided into types. Application of these technics has yielded much new information. It has been shown clearly that certain types of hemolytic streptococci of group A, now causing much disease in military personnel, are incapable of inducing rash formation in persons with positive Dick reactions, who presumably are susceptible.⁶ Strains of these types have been responsible for 90 per cent of all streptococcic infections in certain areas. Furthermore, infection by definitely scarlatinogenic strains has been associated with rash formation in only about 25 per cent of young adults in the armed forces. A similar situation almost certainly exists in the civilian population.

The problem of streptococcic infection of the respiratory tract is therefore that of a disease not associated with a scarlatiniform rash. Insufficient recognition has been afforded this fact, and comprehensive descriptions of the disease are virtually nonexistent, except for those of Bloomfield and his associates,⁷ who have described all the salient features of streptococcic infection, have pointed out that the disease process ordinarily assumes the form of an exudative tonsillitis and have claimed that tonsillectomy confers a high degree of immunity against such infection. It is difficult to add other than further documentation to these excellent descriptions of tonsillitis. The authors did not, however, have the opportunity to study systematically a large number of persons suffering from infection of the respiratory tract in an area in which streptococcic infection was exceedingly common. They were unable, therefore, to determine the frequency of streptococcic

4. Escherich, T., and Schick, B.: *Scharlach*, Vienna, A. Hölder, 1912. Trask, J.: *Scarlet Fever*, in Christian, H. A., and MacKenzie, J.: *Oxford Medicine*, New York, Oxford University Press, 1940, vol. 5, chap. 21, p. 519.

5. Lancefield, R. C.: *Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci*, in *Harvey Lectures, 1940-1941*, Baltimore, Williams & Wilkins Company, 1941, vol. 36, p. 251.

6. Hamburger, M., Jr.; Hilles, C. H.; Hamburger, V. G.; Johnson, M. A., and Wallin, J. G.: *Ability of Different Types of Hemolytic Streptococci to Produce Scarlet Fever*, *J. A. M. A.* **124**:564 (Feb. 26) 1944.

7. (a) Felty, A. R., and Hodges, A. B.: *A Clinical Study of Acute Streptococcus Infection of the Pharyngeal Lymphoid Tissue (Acute Follicular Tonsillitis)*, *Bull. Johns Hopkins Hosp.* **34**:330, 1923. (b) Bloomfield, A. L.: *Streptococcal Infections*, in Blumer, G.: *Practitioners Library of Medicine and Surgery*, New York, D. Appleton-Century Company, Inc., 1933, chap. 15, sect. 2, p. 235. (c) Bloomfield, A. L.: *Differentiation of the Common Varieties of Sore Throat*, *Stanford M. Bull.* **1**:199, 1943.

infection in persons who had undergone tonsillectomies or the importance of exudate as a diagnostic sign in these circumstances.

One critical study of the nature of streptococcic and nonstreptococcic disease has been published.⁸ The authors characterized diseases of the respiratory tract in part and emphasized the fact that exudative tonsillitis may occur in the absence of streptococcic infection. They were greatly handicapped by the fact that the number of patients with streptococcic disease in their group was extremely small. An unfortunate confusion has resulted from their report since the impression was given that the clinical diagnosis of streptococcic infection, even though aided by bacteriologic study of the nasopharyngeal flora, is virtually impossible.

It is the purpose of this paper to present and analyze the clinical and laboratory data obtained during the study of a large number of infections of the respiratory tract occurring in military personnel. The infections will be discussed in groups as they were classified immediately after the completion of the initial clinical and laboratory study, and it will be demonstrated that the accuracy of diagnosis was great. The incidence and the value of the various signs and symptoms of diagnostic importance will be described statistically and a composite picture of each disorder presented. A complete description of the natural history of hemolytic streptococcus infection will be presented elsewhere.

Atypical and confusing examples of both streptococcic and nonstreptococcic disease were frequently discovered, and the general conclusions in the previously mentioned work⁸ were confirmed. These assume a different and clinically more encouraging perspective when considered in relationship to the data obtained in this study of a large number of infections of the respiratory tract, which occurred in an area in which streptococcic disease was common. This probably resembles situations often encountered in the northern United States. In this regard it is important to know that, in spite of the fact that a large number of streptococcic infections occurred during the study period, no true epidemic was established, since fourteen serologic types of streptococci caused infection in more than 5 patients each and a total of twenty-six different types were isolated. Furthermore, the population involved was composed largely of well seasoned troops rather than the new recruits who have been shown repeatedly to be highly susceptible to

8. Commission on Acute Respiratory Diseases: Endemic Exudative Pharyngitis and Tonsillitis, *J. A. M. A.* **125**:1163 (Aug. 26) 1944. Another similar study has been recently described (Keith, J. D., and Carpenter, J.: The Diagnosis of Haemolytic Streptococcal Infection in Acute Nasopharyngitis, *Canad. Pub. Health J.* **37**:127, 1946).

all types of infection of the respiratory tract.⁹ It is believed that the report of our experience more nearly simulates what may be expected in a civilian population than do other descriptions of the disease among military personnel.

METHODS

Plan of Study.—All patients with acute disease of the respiratory tract of any type admitted to a large station hospital were studied. Dispensary physicians ordinarily requested hospitalization for all men with symptoms of disease of the respiratory tract whose temperatures were discovered to be elevated to 100 F. or more. Each patient was seen during the first hospital day by one of us, and the clinical and laboratory studies described in the following paragraphs were instituted.

Clinical Observations.—A history was obtained when each patient was first seen, which was adequate to evaluate the illness. Specific questions were asked in regard to the presence and severity of the following features of the disease, in addition to others:

1. Sore throat, which was rated as 1 plus (slightly sore) to 3 plus (swallowing painful and difficult).
2. Cough.
3. Headache.
4. Chills.
5. Generalized aching.
6. Hoarseness.
7. Coryza.

A physical examination was performed at the same time, special attention being given to the presence of the following signs:

1. Tonsils.
2. Exudate. This sign was graded from 1 plus (small flecks of white material on the tonsils, tonsillar tags or posterior pharyngeal walls) to 3 plus (large confluent areas of white material, often covering the whole tonsil and spreading onto the pharyngeal wall).
3. Abnormal redness of the tonsils and tissues of the anterior and posterior pharynx. This sign was graded from 1 plus (slightly red with engorgement of the blood vessels of the mucosa) to 3 plus (fiery red).
4. Edema of the tonsils and pharyngeal tissues. This sign was graded from 1 plus (slight edema) to 3 plus (massive edema).
5. Tender anterior cervical glands. This sign was graded from 1 plus (definite tenderness of the glands without great enlargement) to 3 plus (the glands greatly enlarged and extremely tender).
6. Scarlatiniform rash.

Cultures of Material from the Throat and the Nose.—The nose and the throat of each patient were swabbed at the time of the initial examination, and cultures were prepared suitable for the isolation of hemolytic streptococci. The methods used will be described elsewhere. Additional swabbings were carried out at

9. Wheeler, S. M., and Jones, T. D.: Factors in the Control of the Spread of Acute Respiratory Infections with Reference to Streptococcal Illness and Acute Rheumatic Fever, *Am. J. M. Sc.* 209:58, 1945.

frequent intervals if hemolytic streptococci were present initially or if the diagnosis remained doubtful. All the isolated hemolytic streptococci were classified serologically into groups and types by means of the precipitin technics of Lancefield.¹⁰

Cultures were recorded as:

1. Negative—No group A hemolytic streptococci recovered.
2. 1 plus—A few group A hemolytic streptococci were isolated.
3. 2 plus—Moderate numbers of hemolytic streptococci were isolated. The predominant flora was composed of other organisms.
4. 3 plus—Many hemolytic streptococci were present and were the predominant organisms, but other organisms were also recovered in considerable numbers.
5. 4 plus—Group A hemolytic streptococci were isolated in very large numbers and were the predominant organisms in the nasopharyngeal flora. Frequently they appeared to be present in pure culture.

All group A hemolytic streptococcus infections will be considered together, regardless of the serologic type of the infectious agent. Full details of the relationship of the type to various clinical and immunologic phenomena will be presented elsewhere.

Leukocyte Counts and Erythrocyte Sedimentation Rates.—The total leukocyte count and the erythrocyte sedimentation (Westergren) rate were determined on the second hospital day for all patients believed to have hemolytic streptococcus infections, for many patients for whom the diagnosis remained doubtful and for a small group of persons in whom definite nonstreptococcic infection had occurred.

Immunologic Study.—The antistreptolysin and the antifibrinolysin of the serum and the plasma of many patients were measured on approximately the second, ninth and twenty-first days of illness by methods described elsewhere.¹¹ Full details of these immunologic observations will be presented in another report. For this report it is necessary only to define the increase of the antibody which has been regarded as significant for the establishment of the etiologic relationship between an infectious disease and the hemolytic streptococci. It is believed that a 50 per cent increment in the antistreptolysin titer or an eight hour prolongation of the time for lysis in the determination of antifibrinolysin is to be regarded as adequate for this purpose.

No details will be given in the body of the paper as to the nature and the degree of the antibody response which, if stated to be present, may be assumed to have involved an increase as great as or greater than that previously described in the amount of the circulating antistreptolysin, the antifibrinolysin or both.

Selection of Cases.—Each hospitalized patient suffering from a disease of the respiratory tract during the study period was examined initially by the technic described earlier. For the purpose of clarity in this presentation, all examples of the common communicable diseases, ulcerative tonsillitis (Vincent's disease) and bacterial or diagnosed primary atypical pneumonia, have been excluded from consideration. Many men in whom the latter disease occurred in a mild and unrecognized form have, without doubt, been included in the group of patients with nonstreptococcic infections.

10. Lancefield.⁵ Most of the typing serums were made available through the generosity of Dr. Rebecca Lancefield.

11. Rantz, L. A., and Randall, E.: A Modification of the Technic for Determination of the Antistreptolysin Titer, *Proc. Soc. Exper. Biol. & Med.* **59**:22, 1945. Boisvert, P. J.: The Streptococcal Antifibrinolysin Test in Clinical Use, *J. Clin. Investigation* **19**:65, 1940.

TABLE 1.—Symptoms and Physical Signs in Patients with Hemolytic Streptococci and Nonstreptococcal Diseases of the Respiratory Tract

	Nonstreptococcal Disease		Group A Carriers		Hemolytic Streptococci Disease with Antibody Response		Hemolytic Streptococci Disease Without Antibody Response		Scarlet Fever		Hemolytic Streptococci Disease, Tonsils Intact		Hemolytic Streptococci Disease, Tonsils Removed	
	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent
Total patients.....	571	100.0	93	100.0	380	100.0	42	100.0	27	100.0	201	100.0	99	100.0
Symptoms														
Sore throat														
Absent.....	416	47.7	47	50.5	24	8.0	2	4.7	1	3.7	12	5.9	12	12.1
1 plus.....	162	18.6	21	22.6	40	13.3	6	14.3	3	11.1	24	10.9	16	16.2
2 plus.....	149	17.1	18	19.4	83	29.4	16	38.1	6	22.6	61	30.3	27	27.2
3 plus.....	144	16.6	7	7.5	148	49.4	18	43.0	17	63.0	104	51.7	44	44.5
Cough														
Present.....	726	83.3	29	31.2	137	42.3	17	40.4	12	45.0	84	41.8	41	41.4
Severe.....	210	24.1	24	25.8	7	2.3	2	4.7	0	0.0	5	2.5	2	2.0
Headache														
Present.....	537	62.3	55	59.1	233	77.8	28	66.6	12	45.0	177	78.1	70	76.6
Severe.....	33	6.8	7	7.5	36	12.0	3	7.1	0	0.0	22	10.9	14	14.1
Generalized aching.....	322	37.0	34	36.8	178	59.4	22	52.4	14	51.9	110	54.6	68	68.7
Coryza.....	316	36.2	34	36.5	65	21.6	9	21.4	8	29.6	47	23.4	18	18.2
Chills.....	241	27.6	26	28.0	180	63.0	19	45.3	18	66.6	121	60.3	68	68.7
Hoarseness.....	115	13.2	10	10.8	3	1.0	0	0.0	0	0.0	1	0.5	2	2.0
Physical signs														
Exudate														
Absent.....	827	95.0	88	94.6	113	37.7	13	30.9	13	48.2	53	26.4	60	60.6
1 plus.....	29	3.3	5	5.4	55	18.3	5	11.9	3	11.1	35	17.4	20	20.2
2 plus.....	12	1.4	0	0.0	73	24.3	8	19.1	6	22.2	58	28.8	15	15.1
3 plus.....	3	0.3	0	0.0	59	19.7	16	38.1	5	18.5	55	27.4	4	4.0
Edema														
Absent.....	562	64.5	56	60.2	43	14.3	5	11.9	5	18.5	22	10.9	21	21.2
1 plus.....	214	24.6	29	31.2	82	27.3	7	16.7	5	18.5	47	23.4	35	35.4
2 plus.....	85	9.7	8	8.6	113	37.7	15	35.7	12	44.5	79	39.3	34	34.3
3 plus.....	10	1.2	0	0.0	62	20.7	15	35.7	5	18.5	53	26.4	9	9.1
Redness														
Absent.....	366	42.0	37	39.9	10	3.3	1	2.4	0	0.0	6	2.9	4	4.0
1 plus.....	298	34.2	32	34.4	39	13.0	3	7.1	4	14.8	22	10.9	17	17.2
2 plus.....	144	16.5	18	19.3	95	31.6	17	40.5	9	33.3	56	27.8	39	39.4
3 plus.....	63	7.3	6	6.4	166	52.0	21	50.0	14	51.9	117	58.3	39	39.4
Adenitis														
Present.....	116	13.6	12	12.9	243	80.9	37	88.1	23	85.2	170	84.6	73	73.8
Severe.....	15	1.7	0	0.0	131	43.6	17	40.5	10	37.0	102	50.8	29	29.3
Height of fever														
Afebrile.....	273	31.4	27	29.1	7	2.3	0	0.0	0	0.0	5	2.5	2	2.0
89 to 99.9 F.....	186	21.4	30	32.1	13	4.3	3	7.1	0	0.0	9	4.5	4	4.0
100 to 100.9 F.....	149	17.1	11	11.8	31	10.3	7	16.7	3	11.1	20	9.9	11	11.0
101 to 101.9 F.....	111	12.7	10	10.8	59	19.6	9	21.4	4	14.8	39	19.4	20	20.2
102 to 102.9 F.....	94	10.8	10	10.8	70	23.3	10	23.8	6	22.2	48	23.8	22	22.2
103 F. and up.....	58	6.5	5	5.4	120	40.0	13	30.9	14	51.9	80	39.9	40	40.5

Eighty-one additional patients, from whose throats hemolytic streptococci of groups other than A were isolated, have not been considered. In certain patients the streptococci were etiologically responsible for the disease process, and in others in whom a "virus type" of disease had occurred they were present fortuitously in the nasopharynx. The presence of such streptococci in the throat constitutes a problem in the study of disease of the respiratory tract and will be discussed elsewhere because of the difficulties of interpretation and for the sake of simplicity.

The remaining patients have been divided into groups exactly as they were classified after the completion of the initial clinical and bacteriologic study. Sixty-eight patients, believed on clinical and bacteriologic grounds to have had hemolytic streptococcus infections, have been omitted because serial antibody determinations were not obtained.

HEMOLYTIC STREPTOCOCCIC INFECTION

Hemolytic streptococci of group A were isolated from the throats or the nasopharynges of 342 men whose disease of the respiratory tract was believed, on clinical grounds, to be the result of infection by these organisms. An antibody response was demonstrated in 300, or 87.7 per cent, of the patients, indicating that the diagnosis was usually accurate. Those in whom an increase in antibody failed to develop cannot be proved to have streptococcic disease, but it is known¹² that in from 10 to 20 per cent of all instances of scarlet fever the patients fail to exhibit an antistreptolysin or antifibrinolysin response. Infection by streptococci cannot be excluded on the basis of the study of these antibodies. The critical clinical study is based on the 300 patients in whom the disease was proved to be streptococcic, but the data obtained for the additional 42 are included for inspection by interested persons. There is a striking parallelism between the manifestations of the infectious process in the two groups.

The significant data obtained during this study of group A hemolytic streptococcus infection are presented under various categories in the last five columns of tables 1 and 2. This information will now be described and discussed.

Symptoms.—Sore throat was the most characteristic symptom of hemolytic streptococcus disease of the respiratory tract. It was severe or extremely severe in 78.8 per cent of all patients. Swallowing was unusually difficult for these men, and even fluids were frequently refused. The frequency of occurrence of this symptom is indicated by the fact that it was absent in only 8 per cent of all patients.

12. Mote, R. J., and Jones, T. D.: Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever and Rheumatoid Arthritis: II. The Frequency of Antistreptolysin "O," Antifibrinolysin and Precipitating-Antibody Responses in Scarlet Fever, Hemolytic Streptococcal Infections and Rheumatic Fever, *J. Immunol.* **41**:35, 1941.

TABLE 2.—Laboratory Data for Patients with Hemolytic Streptococci and Nonstreptococcal Diseases of the Respiratory Tract

	Nonstreptococcal Disease		Group A Carriers		Hemolytic Streptococcal Disease with Antibody Response		Hemolytic Streptococcal Disease Without Antibody Response		Scarlet Fever		Hemolytic Streptococcal Disease, Tonsils Intact		Hemolytic Streptococcal Disease, Tonsils Removed	
	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent
Cultures of material from the throat														
Number studied.....	871	100.0	93	100.0	300	100.0	42	100.0	27	100.0	201	100.0	99	100.0
Negative.....	871	100.0	3	3.3	3	1.0	0	0.0	0	0.0	3	1.5	0	0.0
1 plus.....	0	0.0	20	21.5	4	1.3	1	2.4	2	7.4	3	1.5	1	1.0
2 plus.....	0	0.0	39	41.9	20	6.7	3	7.1	4	14.8	12	5.9	8	8.1
3 plus.....	0	0.0	13	14.0	29	9.7	6	14.3	4	14.8	20	9.9	9	9.1
4 plus.....	0	0.0	18	19.3	244	81.3	32	76.2	17	63.0	163	81.1	81	81.7
Cultures of material from the nose														
Number studied.....	825	100.0	56	100.0	239	100.0	49	100.0	25	100.0	193	100.0	96	100.0
Positive.....	0	0.0	11	19.6	190	65.7	19	48.7	19	76.0	122	63.2	68	70.9
Leukocyte count														
Number studied.....	53	100.0	20	100.0	299	100.0	42	100.0	27	100.0	201	100.0	98	100.0
Less than 9,000 per cu. mm.....	25	47.2	13	65.0	69	23.1	14	33.3	5	18.5	43	21.4	26	26.5
9,100 to 12,900 per cu. mm.....	23	43.4	6	30.0	83	27.8	11	26.2	6	22.2	53	26.4	30	30.6
13,000 to 15,900 per cu. mm.....	5	9.4	1	5.0	67	22.4	12	28.6	6	22.2	49	24.4	18	18.7
16,000 per cu. mm. and over.....	0	0.0	0	0.0	80	26.7	5	11.9	10	37.0	56	27.8	24	24.5
Erythrocyte sedimentation rates (Westergren)														
Number studied.....	47	100.0	20	100.0	294	100.0	41	100.0	26	100.0	198	100.0	96	100.0
Less than 9 mm. per hour.....	17	36.1	12	60.0	26	8.8	6	14.6	4	15.4	19	9.6	7	7.3
9 to 19 mm. per hour.....	16	34.1	3	15.0	60	20.4	9	21.9	8	30.8	39	19.7	21	21.9
20 to 29 mm. per hour.....	6	12.8	4	20.0	61	20.7	14	34.1	4	15.4	43	21.7	18	18.7
30 to 39 mm. per hour.....	2	4.2	1	5.0	51	17.5	4	9.8	3	11.5	31	15.6	20	20.8
40 to 49 mm. per hour.....	3	6.4	0	0.0	39	13.3	3	7.3	5	19.2	24	12.1	15	15.6
50 mm. per hour and over.....	3	6.4	0	0.0	57	19.4	5	12.2	2	7.7	42	21.2	15	15.6

Headache (77.8 per cent), generalized aching (59.4 per cent) and chills (63 per cent) were the most common complaints. Forty-two and three-tenths per cent of the men coughed, but only 2.3 per cent did so severely. Hoarseness was notable by its rarity (1 per cent) in this group of patients.

Physical Signs.—Tonsillar and pharyngeal exudate has usually been regarded as the characteristic sign of streptococcic infection of the respiratory tract and was a prominent feature of the disease as observed during this study. It was present in small amounts in the throats of 18.3 per cent and in large amounts in 44 per cent of all patients. Much more notable is the fact that no exudate was seen for 37.7 per cent of these patients with proved hemolytic streptococcus infection.

Previous authors have described edema of the pharyngeal tissues in patients with streptococcic sore throats but have not sufficiently emphasized its frequency or its value as a diagnostic sign. Easily recognizable and characteristic swelling and edema of the tonsils, anterior and posterior pillars, soft palate and uvula were observed in 85.7 per cent of this group. Exudate was not present in many of these patients. Very often the encroachment of the engorged tissues on the faucial space was exceedingly great, and the airway itself was sometimes endangered. Lesser degrees of edema are, however, easily recognized by the inexperienced observer.

Most characteristic of all the pharyngeal signs of streptococcic infection was the abnormal redness of the palate, anterior pillars and other pharyngeal tissues, which was absent in only 3 per cent and present to an extreme degree in 83.6 per cent of all the patients. The fiery redness present in slightly more than half is unmistakable and very valuable in differential diagnosis. Considerable experience is, unfortunately, required in the interpretation of the lesser degrees of abnormality. It is important to note and distinguish between the various gradations of this sign since pronounced redness of the pharyngeal tissues may be observed in the absence of exudate or severe edema.

Tenderness of the anterior cervical glands was discovered to be the single most useful and reliable sign of infection of the throat by hemolytic streptococci since it is readily recognized and accurately interpreted by any physician. Tender glands were observed in 80.9 per cent and were very abnormal in 43.6 per cent of the patients in this group. The adenitis was usually bilateral, but only one side was affected in many instances. It is probably correct to state that more information could be obtained rapidly as to the frequency of streptococcic infection among a number of patients with acute infection of the respiratory tract by the palpation of the glands in the neck than by an examination of the throat.

Fever was noted during the hospital stay of nearly all of these patients, as was to be expected, since afebrile patients were not admitted. It is obvious that the height of the elevation of temperature cannot be used as a differential sign in the diagnosis of respiratory disease, but two points deserve emphasis. Men infected by streptococci were more noticeably febrile on the whole than were those men suffering from nonstreptococcic disease, but there were a considerable number of the former in whom only low grade fever was observed. Entirely afebrile patients with hemolytic streptococcus infection have been described elsewhere.¹³

Laboratory Studies.—The results of the study of the throat flora are of importance since hemolytic streptococci were present in very large numbers and as the predominant organism in 90.9 per cent and in moderate numbers in an additional 6.7 per cent of the patients in whom an antibody response was demonstrated. Very few or no hemolytic streptococci were discovered in the throats of 7 typical patients, in all of whom the causative agent was recovered from the nose. No explanation can be offered for this phenomenon other than that some technical errors inherent in swabbing the throat and in the preparation of cultures were made.

Cultures of material from the nose were made for nearly all these patients. Hemolytic streptococci were isolated in 65.7 per cent and were usually present in nearly pure culture. This procedure is of some value since inexperienced laboratory technicians are more likely to isolate and identify satisfactorily the causative agent in these circumstances. The culture of material from the nose is also much less likely to be positive in cases in which a "virus type" infection has occurred in a person who previously was a carrier of hemolytic streptococci.

The total leukocyte count was increased in 76.9 per cent of the cases of streptococcic infection but sufficiently so to be of diagnostic value (above 13,000 per cubic millimeter) in only 49.1 per cent. The erythrocyte sedimentation rate was accelerated in 91.3 per cent and was greater than 20 mm. per hour in 70.8 per cent of this group. Very often rates greater than 40 mm. per hour were recorded.

Effect of Tonsillectomy.—Bloomfield^{7b} has previously stated that tonsillectomy confers a considerable degree of protection against infection of the respiratory tract by hemolytic streptococci. This was not the case in the group described in this report since the tonsils had been removed with equal frequency in men suffering from streptococcic infections and men with nonstreptococcic infections. Tonsillectomy had

13. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcus Sore Throat: A Detailed Study of the Simultaneous Infection of a Large Number of Men by a Single Type, Arch. Int. Med. 76:278 (Nov.-Dec.) 1945.

been performed on 33 per cent of the men in the former and 34.4 per cent of men in the latter group.

It is probable that the relationship between the presence of tonsils and streptococcic infection varies according to the types of strains of the organisms. More important is the striking effect of the absence of tonsils on the clinical manifestations of streptococcic infections of the respiratory tract. An inspection of columns six and seven of tables 1 and 2 shows that the symptoms of streptococcic infection in men with and men without tonsils are similar, as are the laboratory data, but the physical signs in the throat are different in the two groups. Exudate was demonstrated more frequently and in larger amounts in patients whose tonsils were intact; it was absent or present in minimal amounts in 80.8 per cent of the patients whose tonsils had been removed. The magnitude and the frequency of edema of the pharyngeal tissues were also less in the absence of tonsils, but the difference was not so striking.

Definite abnormal redness of the palate, anterior pillars and other pharyngeal tissues and tenderness of anterior cervical glands were the two manifestations of streptococcic infection observed as often in the absence as in the presence of tonsils. These signs are, therefore, of the greatest diagnostic importance.

Scarlet Fever.—A scarlatiniiform rash was observed in 27 persons infected by hemolytic streptococci. The essential data obtained from these patients have been presented separately in column 5 of tables 1 and 2 for the purpose of emphasizing the essential similarity between patients with and those without rash. The tonsils had been removed from 15, or 55.5 per cent, of these men. When this fact is considered in relationship to the symptoms, the physical signs and the laboratory observations, it will be observed that the presence of a rash had no effect on the clinical nature of streptococcic infection of the respiratory tract. Somewhat higher temperatures were noted in association with a rash, but the differences in this respect between this group and the patients without rash were not great.

Atypical Streptococcic Disease.—It has been pointed out that the absence of tonsils greatly alters the physical signs of hemolytic streptococcus infection of the respiratory tract. A further elaboration of the problem of diagnosis of atypical infections is desirable. Exudate on the tonsils or tonsillar tags in association with other of the signs of streptococcic disease, described previously, and the demonstration of large numbers of group A hemolytic streptococci in the flora of the throat usually permitted the diagnosis of infection by these organisms. The problem was more difficult with the 37.7 per cent of all patients in whom exudate was not demonstrable. Edema, abnormal redness and adenitis assisted in the differentiation of three quarters of this group.

Nasopharyngeal signs were minimal in 33 men in whom an anti-streptococcic antibody response occurred—a summary of the physical signs is presented in table 3. Tonsillectomy had been performed in 19, or 57.5 per cent.

The infections of 19 patients were properly classified principally on the basis of tender anterior cervical glands and the presence of large numbers of group A streptococci in the throat flora. Intense redness of the pharyngeal tissues of 5 patients was helpful. An additional 14 patients were considered, after the initial study, to have streptococcic infection, in spite of a paucity of signs which obviously did not allow accurate diagnosis in the absence of studies of antibody levels. Such patients will be further discussed in another section.

The principal feature to be emphasized is that febrile hemolytic streptococcus infection of the respiratory tract may occur in persons who exhibit only the most trivial abnormalities in the throat and that

TABLE 3.—*Physical Signs in Patients with Atypical Hemolytic Streptococcic Disease of the Respiratory Tract*

Number of Patients	Exudate	Edema	Redness	Adenitis	Tonsillectomy
4.....	0	0	0	0	3
3.....	0	0	0	1-2+	0
5.....	0	0	1+	0	3
3.....	0	1+	1+	0	2
4.....	0	0	1+	1-2+	3
7.....	0	1+	1+	1-2+	5
2.....	0	0	2+	0	0
5.....	0	0	2+	1-2+	3

tender glands will often be the critical sign in such patients. At least 5 to 10 per cent of all hemolytic streptococcus infections will be clinically indistinguishable from the "virus type" disease of the respiratory tract.

Composite Picture of Hemolytic Streptococcic Infection.—Hemolytic streptococcic infection of the respiratory tract, as observed during this study, was a febrile illness usually of acute onset and associated with the expected manifestations of such a disorder, including chills, headache, generalized aching and variable degrees of prostration. Many patients were excluded by the artificial method of selection, which required the presence of fever as an indication for hospitalization, and it must be constantly borne in mind that mild and inapparent infections are probably extremely common.

The characteristic symptom was sore throat, which was rarely absent and ordinarily severe. Cough and coryza were often present but were usually not prominent complaints. The rarity of hoarseness was notable.

Clinically typical hemolytic streptococcus sore throat was observed most frequently in men whose tonsils were intact and was characterized by varying amounts of tonsillar and pharyngeal exudate and varying

degrees of redness and edema of the pharyngeal tissues. In addition, tender anterior cervical glands were nearly always noted. It will be demonstrated later that the concatenation of these signs permits diagnosis of hemolytic streptococcus infection with a high degree of accuracy, even without a bacteriologic study of the flora of the throat.

A large number of patients remained, however, for whom the making of a diagnosis was more difficult since certain of these signs, particularly exudate, were absent. This was especially so if the tonsils had been removed. No difficulty arose if severe pharyngeal edema was observed in such patients, but there were approximately 10 per cent of the whole group with proved streptococcic infections in whom no or only minimal swelling of the throat could be discerned. In such persons tender glands in the neck, abnormal redness of the throat and large numbers of hemolytic streptococci in the nasopharyngeal flora permit a reasonably accurate differentiation from other types of infection of the respiratory tract. A certain number of adult patients with infections of the respiratory tract will always be discovered for whom a definite diagnosis cannot be made on clinical grounds, even though large numbers of group A hemolytic streptococci are recovered from the throat. The magnitude of this group will vary with the geographic area, the epidemic state of the community and the skill and the experience of the examining physician. Other aspects of this problem will be discussed later in the paper.

Moderate to large numbers of group A hemolytic streptococci were discovered in the throat flora of nearly all these patients with proved streptococcic infection. These organisms frequently appeared to be present in almost pure culture. Their absence in a few instances may possibly be explained on the basis of errors in the technics used in obtaining material for culture.

The total number of white blood cells and the erythrocyte sedimentation rate were usually increased in cases of hemolytic streptococcus sore throat, but both values were, unfortunately, often within normal limits in the cases presenting difficult problems in diagnosis.

NONSTREPTOCOCCIC INFECTION

Hemolytic streptococci were never isolated from the nasopharynxes or throats of 871 patients with the symptoms and signs of disease of the respiratory tract. The infectious agents involved may well have been of a diverse nature but all such patients have been grouped together as having nonstreptococcic infections of the respiratory tract. The essential data obtained from these patients are presented in column 1 of tables 1 and 2.

This group of patients was very different clinically from those infected by hemolytic streptococci. The general symptoms of a febrile

illness were usually observed. Sore throat was, however, minimal or not present in the majority (66.3 per cent). Careful questioning often revealed that the pain on swallowing was caused by a disturbance, during this act, of an inflamed and tender larynx rather than by the edema of the pharyngeal tissues which is characteristic of streptococcic infection. Cough, which had not been a prominent feature of the symptom complex of the previous group, was present in 83.3 per cent and severe in 24.1 per cent. Definite hoarseness was noted in 13.1 per cent.

Great dissimilarity also existed between the physical signs of persons with streptococcic and those of persons with nonstreptococcic disease of the respiratory tract. Exudate was not detected in the throats of 95 per cent of the latter group. It was present in minimal amounts in 3.3 per cent but was not often associated with other abnormalities suggesting streptococcic infection, and was usually a thinner, more slimy material than that seen when hemolytic streptococci were the causative agents. There were 15 patients in whom large amounts of tonsillar exudate were observed but no hemolytic streptococci were discovered in the throat. Special comment will be made later on these patients.

Edema and abnormal redness of the nasopharyngeal tissues were minimal or not present in all but 10.9 per cent and 23.8 per cent, respectively, of all patients with nonstreptococcic disease of the respiratory tract. Adenitis was present in 13.6 per cent of these men but was severe in only 1.7 per cent.

The clinical laboratory investigation of this group of patients was incomplete, but it is clear that the total leukocyte count in cases of nonstreptococcic disease is rarely greater than 13,000 per cubic millimeter and that the erythrocyte sedimentation rate is usually less than in the previously described cases.

Patients with Atypical Infections.—Roughly 10 per cent of the total group with definite nonstreptococcic diseases presented signs suggesting infection by hemolytic streptococci. Most of these had noticeable edema and redness of the pharyngeal tissues, associated with tenderness of cervical glands. Such patients may be distinguished with certainty from other similar ones in whom streptococcic infection has occurred only if group A streptococci are not demonstrated to be present in the nasopharynx.

There were 15 patients with exudative tonsillitis in the study group in whom great edema and redness of the pharyngeal tissues and marked tenderness of cervical glands were also present. Repeated examinations failed to reveal hemolytic streptococci in the throat, and no antistreptococcic antibody response occurred in those in whom serial determinations were carried out.

In summarizing, 10 per cent of the patients with nonstreptococcic disease in whom exudate was not observed presented signs suggesting streptococcic infection. The infections of approximately 25 per cent of all patients in whom any amount of exudate was demonstrated and 10 per cent of those in whom exudate was present in large amounts were not of streptococcic origin.

Infection in Hemolytic Streptococcus Carriers.—Group A hemolytic streptococci were present in the throats of from 5 to 20 per cent of the healthy camp population. It was to have been expected, therefore, that these organisms would be demonstrated in the flora of the throats of a considerable number of men who were believed, on clinical grounds, to be suffering from "virus type" infection. This situation arose in 93 patients, 33 of whom harbored hemolytic streptococci in large numbers. The essential data from this group are presented in column 2 of tables 1 and 2. An inspection of this material shows that the disease of these patients resembled clinically the most typical examples of nonstreptococcic infection.

Exudate in only small amounts was present in 5 and slight tenderness of cervical glands in 12 patients. Large numbers of group A hemolytic streptococci were recovered from the throats of only 33.3 per cent of these men in contrast to 90 per cent of those proved to have been infected by these organisms. Serial antibody studies were carried out for 19 of these patients who harbored many hemolytic streptococci, and a response was demonstrated in only 2 of them. The separation of these men into a group was justified, although an error of 5 to 10 per cent was made.

The clinical resemblance of the disease of these patients to "virus type" infection was to be expected from the method of selection since the presence of hemolytic streptococci in the throat flora of a person presenting signs suggesting such infection naturally led to the classification of the infection as streptococcic. That errors were made during this process is obvious, because a group of patients has just been described in whom the physical signs of nonstreptococcic disease resembled closely those seen during streptococcic infection. Such a process occurring in a carrier of hemolytic streptococci would usually be believed to be an instance of infection by these organisms. These are, of course, included in the group classified as having hemolytic streptococcus disease of the respiratory tract without antibody response.

No method is available at present for differentiating the nonstreptococcic infection of the respiratory tract which occurs in a hemolytic streptococcus carrier with absolute certainty. The error will be small if both clinical and bacteriologic studies are undertaken. Ten per cent of nonstreptococcic infections resemble clinically those caused by streptococci. Ten to 20 per cent of them may occur in persons who

were previously carriers of hemolytic streptococci. One to 2 per cent of nonstreptococcic infections of the respiratory tract will, therefore, be believed erroneously to be instances of streptococcic disease.

Composite Picture of Nonstreptococcic Infection.—Nonstreptococcic disease of the respiratory tract as observed during this study was typically a disorder associated with cough and often with hoarseness. Physical examination usually revealed nearly normal nasopharyngeal tissues. Exudate, edema and abnormal redness were present to a minimal degree or were absent. Tender anterior cervical glands were rarely observed. A total leukocyte count of less than 13,000 per cubic millimeter and a normal or only moderately elevated erythrocyte sedimentation rate were observed. The characteristic features permitted the satisfactory identification of at least 90 per cent of all patients with nonstreptococcic infection. The others presented a more difficult problem.

Typical exudative tonsillitis occurred in a small number of men in the absence of nasopharyngeal hemolytic streptococci or of an anti-streptococcic antibody response. In others edema, abnormal redness and adenitis with tenderness of the involved glands were discovered. If group A hemolytic streptococci were not recovered from the throat, these patients could be readily differentiated. Hemolytic streptococci were, however, often discovered in the nasopharyngeal flora of men with nonstreptococcic infection of the respiratory tract because these organisms were harbored in the throats of from 5 to 20 per cent of the various camp population groups.

When the "virus type" infection supervened in one of these carriers and presented typical clinical features, the diagnosis could be made with only small risk of error, particularly if hemolytic streptococci were present in small numbers. When the signs and symptoms were those usually seen in patients with streptococcic disease and hemolytic streptococci were isolated in relatively large numbers, a satisfactory differentiation could not be made. This situation has been shown to have prevailed in from 1 to 2 per cent of all instances of nonstreptococcic disease of the respiratory tract.

COMMENT

The clinical differentiation of streptococcic and nonstreptococcic diseases of the respiratory tract is not difficult when each occurs in its typical form. The contrast between the person to whom each swallow is agony, whose pharynx is red and edematous, whose tonsils are covered with exudate and whose cervical glands are large and tender and another who is hoarse and coughing and whose throat and neck are almost normal on physical examination is too striking to be missed by the most inexperienced physician. An error of only 10 per cent

was introduced in each group during the study just described if such characteristic infections were classified without bacteriologic study of the flora of the throat.

Considerable variation from these extreme cases may occur and still permit accurate separation into clinical groups, particularly if it be borne in mind that streptococcic infection may frequently occur without the formation of demonstrable exudate. A study of the throat flora will usually be necessary in these circumstances if maximal accuracy of diagnosis is to be attained. The recovery of large numbers of hemolytic streptococci from the nasopharynx of a person in whom moderate redness and edema of the pharyngeal tissues and tenderness of anterior cervical glands have been demonstrated makes imperative a diagnosis of hemolytic streptococcus infection.

There will remain a considerable number of patients suffering from infection of the respiratory tract who will be difficult to classify even after careful study of the throat flora. A few of these will have exudative tonsillitis of unknown cause. The more important portion will be composed of patients whose illness clinically resembles a "virus type" disease but in whom hemolytic streptococcus infection has occurred. It may be quite impossible to distinguish between certain of the latter group and those patients in whom a nonstreptococcic infection has supervened in a group A hemolytic streptococcus carrier. Reexamination of the patient and reinterpretation of the clinical laboratory data after the results of cultures of material from the throat are known may enhance the accuracy of classification.

Occasionally the presence of a scarlatiniform rash will be of value in differential diagnosis. The occurrence of such a rash is to be regarded only as an interesting manifestation of hemolytic streptococcus infection. Its presence does not indicate that the patient will be more severely ill, require more elaborate therapy or be more susceptible to suppurative and nonsuppurative complications than a person with a similar infection in whom a rash does not develop.¹⁴

No technics are available at present for the absolute differentiation of streptococcic and nonstreptococcic infection of the respiratory tract. The serial measurement of antistreptococcic antibodies will not accomplish this since an increase in these substances will not be demonstrable in a considerable number of patients with definite hemolytic streptococcus infection.

The problem presented by the approximately 5 per cent of all patients from whose throats hemolytic streptococci not of group A were isolated has not been considered in this discussion. About one

14. One of us (W. W. S.) feels that this statement is in part incorrect, since he believes that the severe forms of hemolytic streptococcus disease of the respiratory tract with rash should usually be treated with scarlet fever antitoxin.

third of these are believed to have been infected by members of groups C and G. The others were probably fortuitously present in the throats of persons with nonstreptococcic disease. The occasional discovery of these relatively less pathogenic streptococci in large numbers in the nasopharyngeal flora of patients suffering from disease of the respiratory tract may lead to confusion, since the ordinary clinical bacteriologic laboratory is not prepared to distinguish between the various serologic groups of hemolytic streptococci.

It is our opinion, based on the study described in this paper and on observations in civilian groups, that a differentiation between streptococcic and nonstreptococcic diseases of the respiratory tract in adults may be made in northern United States with an accuracy of approximately 70 per cent without bacteriologic study of the throat flora and in from 80 to 90 per cent if this laboratory procedure is included. The situation is probably different in the southern states, where streptococcic disease occurs infrequently. In these circumstances the atypical varieties of nonstreptococcic disease would be observed relatively more often and differential diagnosis would be correspondingly more difficult.

Satisfactory differential clinical diagnosis of acute nonpneumonic disease of the respiratory tract therefore requires information as to the nature of the infectious processes which occur commonly in a particular geographic area, experience in the interpretation of the abnormalities in the pharyngeal tissues and neck which may occur as the result of such infections and an adequate bacteriologic study of the nasopharyngeal flora.

MEGAKARYOCYTIC REACTION LOCALIZED IN THE BONE MARROW

Report of a New Hematologic Syndrome with Observations on the Origin and Development of Megakaryocytes and on the Derivation of Platelets

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HITHERTO there have been only two diseases known in which the megakaryocytes occupy the center of the pathologic picture. One is thrombopenic purpura, in which these cells suffer an injury. The other is chronic aleukemic myelosis, characterized by an extra-medullary megakaryopoiesis. A case of acute megakaryoblastic leukemia, the only one so far recorded in the literature, was described by von Boros.¹ However, its authenticity is doubted by some hematologists.² In other lesions in which these bone marrow cells are involved, such as in chronic myeloid leukemia, hyperthyroidism and polycythemia, they merely play a secondary role.

In the present case the megakaryocytes were the elements affected principally and in a manner unique in hematologic history. It is reported, also, because of the light it throws on the problems concerning the origin and maturation of megakaryocytes and the derivation of platelets from them.

REPORT OF A CASE

G. M., a Filipino housewife, was admitted to the charity ward of San Juan de Dios Hospital on Oct. 14, 1940, complaining of headache and fever with general bodily weakness.

For about a year previous to the present illness she had been suffering from amenorrhea. More recently palpitation and precordial pain supervened which sometimes prevented her from continuing the day's work. Occasionally this precordial pain would become so severe that breathing was rendered difficult. Dizziness accompanied it now and then. For these complaints she did not seek any medical aid.

A week prior to the date of admission, she fell ill with severe cephalalgia, which she attributed to delayed meals and to baths at improper times. Three days later she had a chill followed by fever, which lasted till the ninth day of her

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1. von Boros, J.: Ueber einen Fall von akuter Megakaryoblastenleukämie, Ztschr. f. klin. Med. **118**:697, 1931.

2. (a) Stransky, E.: Personal communication to the author. (b) Forkner, C. E.: Leukemia and Allied Disorders, New York, The Macmillan Company, 1938, p. 184.

stay in the hospital. According to her, the chill occurred for only about a minute. Additional complaints were anorexia and general debility.

Physical Examination.—Physical examination on the day of entrance revealed very pale conjunctivas, eruptions at the right angle of the mouth and visible pulsation of the cervical vessels. Tactile fremitus was diminished on the right side over the infrascapular region. On the same area pulmonary resonance was impaired and vesicular breathing noticeably diminished. A faint systolic murmur was heard over all the valvular areas except over the tricuspid valve. There were no other abnormal pulmonary and cardiac observations. Lymph nodes were not enlarged. The liver and spleen were not palpable. There were no petechial hemorrhages, no jaundice and no pain over the bones and joints. The blood pressure was 100 systolic and 65 diastolic, the temperature 38.8 C. (101.8 F.), the radial pulse rate 98 beats per minute and the respiration rate 30 per minute.

There were no complaints involving other systems.

Past History.—The past history disclosed an attack of influenza and another disease simulating acute rheumatic fever. She had not suffered from any appreciable loss of blood, and had never been hospitalized before.

Résumé of Laboratory Examinations.—During her forty-four day sojourn in the hospital, five routine examinations of the urine, eight of the blood and seven of the feces were made. In the first four urinary examinations (made on October 19, 24 and 29 and November 5) albumin in moderate amount, with granular casts (1 plus) and hyaline casts (1 plus) was detected. Pus cells (4 plus) and erythrocytes (1 to 3 plus) were also encountered. The fifth examination (November 28) showed normal urine. The specific gravity in all examinations was consistently within the normal range.

All examinations of the feces disclosed ova of *Trichuris trichiura* and of *Ascaris lumbricoides*. No ova of *Ankylostoma* were seen.

Four examinations for occult blood in the stools gave negative results.

The first examination of the blood (October 18) showed a hemoglobin content of 60 per cent (Tallqvist), 2,675,000 red cells per cubic millimeter and 16,200 white cells. The differential count was as follows: 80 per cent polymorphonuclear leukocytes, 18 per cent lymphocytes and 2 per cent monocytes.

In subsequent examinations, the hemoglobin values oscillated between 55 and 70 per cent, the red blood cells between 2,950,000 and 3,380,000 and the white blood cells between 25,500 and 4,250 per cubic millimeter; the polymorphonuclears oscillated between 81 and 60 per cent, the lymphocytes between 17 and 38 per cent, the monocytes between 1 and 3 per cent and the eosinophils between 0 and 2 per cent.

Platelets were counted four times, the number ranging from 200,000 to 290,000 per cubic millimeter.

Serologic examination yielded an icterus index of 2 and a Widal reaction positive up to a dilution of 1:320 (2 plus). Culture for *Bacillus typhosus* was negative.

Roentgenographic examination of the skull and sternum showed no pathologic changes of the bone.

Temperature Curve.—During the first eight days of hospitalization the patient had a remittent fever. The chart showed four peaks occurring on the second (39.9 C. [103.8 F.], sixth (39.8 C. [103.6 F.], seventh 39.8 C. [103.6 F.]) and eighth (39.5 C. or 103.1 F.) days. Between peaks the temperature dropped slightly but did not touch normal. On the ninth day the fever disappeared, and throughout the rest of her sojourn she remained afebrile, except for an occasional slight 0.1 to 0.4 degree [C.] rise of temperature above the normal occurring, at noon.

Treatment.—Santonin and a purgative were routinely administered on the first day and quinine and methenamine during fever. Later the patient was given iron and ammonium citrates, in doses of 6 Gm. daily, till her discharge.

Comment.—Although the Widal test yielded a positive result, the diagnosis of typhoid was rejected by the attending physician on account of the inconsistent clinical observations and the results of the examination of the blood. Pyelitis was the diagnosis given for the febrile condition.

The remainder of the patient's days in the hospital were given to the treatment of her anemia. However, the red blood cells did not increase beyond 3,380,000 per cubic millimeter. This unexplained anemia is the theme of this report.

Follow-Up.—Six months after the patient's discharge from the hospital (May 28, 1941) I examined her. She was still pale and complained of weakness. However, she was able to carry on her usual household duties. She was pregnant at the time. The lungs and heart were apparently normal, and the spleen and liver were not palpable. No pains were felt over the bones. No recurrence of the febrile ailment for which she had been hospitalized before existed. Specimens of peripheral blood were secured for various examinations. She refused to permit a sternal puncture at this time.

HEMATOLOGIC PICTURE

In connection with my studies of the blood, I secured a specimen of the sternal marrow. The unexpected presence of numerous megakaryocytes in the smear led me to make a more detailed study of the case. My examinations gave the following results, arranged in chronologic order:

On Oct. 20, 1940 the patient's temperature was 38.4 C. (101.1 F.). A cell count of bone marrow from the manubrium of the sternum showed 596,000 nucleated cells per cubic millimeter with the following differential distribution: myeloblasts, 5.4 per cent; premyelocytes, 17 per cent; basophils, 1.4 per cent; eosinophils, 8.2 per cent (myelocytes, 1.7 per cent; juvenile form, 2.5 per cent; stab forms 0.9 per cent, and segmented forms, 3.1 per cent); neutrophils, 63.5 per cent (myelocytes, 14.9 per cent; juvenile forms, 20.7 per cent; stab forms, 17.5 per cent, and segmented forms, 10.4 per cent); lymphocytes, 3.5 per cent; monocytes, none, and mitotic white blood cells, 1 per cent. There were 164 nucleated red cells counted for every 350 white cells. Of the former 12 were proerythroblasts, 21 basophilic erythroblasts, 13 macroblasts, 105 normoblasts, 8 mitotic red cells and 5 megalo-blasts. The myeloid-erythroid ratio was 2.1:1. There were 4,000 megakaryocytes counted for every 1,000,000 nucleated bone marrow cells. No specimen of the peripheral blood was taken on this day.

On Oct. 22, the patient's temperature was normal. The Schilling hemogram was: basophils, 0.4 per cent; eosinophils, 1.4; myelocytes, 1.6 per cent; juvenile forms, 1.6 per cent; stab forms, 30.8 per cent; segmented forms 47.2 per cent; lymphocytes, 13.8 per cent, and monocytes, 3.2 per cent. There was 1 normoblast for every 250 white blood cells. Moderate anisocytosis and poikilocytosis and pronounced rouleaux formation were noted. Many of the lymphocytes showed more basophilic cytoplasm than ordinarily observed; their nuclei displayed tendency to blocking. Vacuoles were observed in the cytoplasm of the monocytes. No unusual features were noted in the granulocytes. Platelets were numerous and of three varieties (to be described later). No megakaryocytes were found. The reticulocyte count was 15 for every 1,000 red blood cells.

On October 30, although the liver and spleen were not enlarged, attempts were made to puncture them. The attempt on the latter failed. Examination of the material secured from the liver yielded nothing significant.

On November 2 the patient's temperature was normal. Bone marrow from the sternum contained 595,000 nucleated cells per cubic millimeter. The differential count was as follows: myeloblasts, 4.8 per cent; premyelocytes, 11.6 per cent; basophils, 0.4 per cent; eosinophils, 2.4 per cent (myelocytes, 1.2 per cent; juvenile forms, 0.8 per cent; stab forms, 0 per cent, and segmented forms, 0.4 per cent); neutrophils, 74.4 per cent (myelocytes, 19.6 per cent; juvenile forms, 24.8 per cent; stab forms, 26.4 per cent, and segmented forms, 3.6 per cent); lymphocytes, 3.6 per cent; monocytes, 1.2 per cent, and mitotic white blood cells, 1.6 per cent. Two plasma cells were counted for every 250 white blood cells. Eighty-six nucleated red blood cells were counted for every 250 white blood cells. Of the nucleated red blood cells, 6 were proerythroblasts, 2 basophilic erythroblasts, 5 macroblasts, 69 normoblasts, 3 mitotic red blood cells, and 1 megaloblast. The myeloid-erythroid ratio was 2.9:1. Two thousand, five hundred and fifty-eight megakaryocytes were counted for every 1,000,000 nucleated marrow cells.

On November 11, the patient's temperature was normal. The Schilling hemogram was: basophils, 1.2 per cent; eosinophils, 0.8 per cent; myelocytes, 0.8 per cent; juvenile forms, 1.6 per cent; stab forms, 23.2 per cent, and segmented cells, 33.6 per cent; lymphocytes 36.4 per cent; plasma cells, 0.4 per cent, and monocytes, 2.0 per cent. Platelets were still numerous. The condition of the red blood cells was practically the same as that on October 22. No megakaryocytes were found.

On November 12 the Wintrobe values were as follows: hemoglobin (Dare), 6.37 Gm. per hundred cubic centimeters of blood; red cells, 3,800,000 per cubic millimeter; volume of packed cells, 21.8 cc. per hundred cubic centimeters of blood; mean cell volume, 57 cubic microns, and mean cell hemoglobin, 16.7 micro-micrograms.

Follow-up study on May 28, 1941, yielded the following results: The hemoglobin was 50 per cent (Tallqvist); red cell count was 3,455,000 per cubic millimeter, and white cell count was 7,850 per cubic millimeter. There were between 185,000 (Rees-Ecker) and 186,570 (Fonio) platelets per cubic millimeter. The coagulation time was six and one-half minutes (Lee and White). The icterus index was 3.1 units. The bleeding time was two and one-half minutes (Duke). Clot retraction was normal.

The Schilling hemogram was: basophils, 0 per cent; eosinophils, 4 per cent; myelocytes, 0 per cent; juvenile forms, 0 per cent; stab forms, 12 per cent; segmented forms, 33 per cent; lymphocytes, 48 per cent, and monocytes, 3 per cent. Platelets were not as numerous as before, but the same three varieties existed among them. No megakaryocytes were found.

Comment: A 14 B. D. special needle was used for the sternal puncture. Less than 0.5 cc. of bone marrow was secured each time. The cell count was made by placing a drop of the material on a slide with the ordinary white cell pipe. Direct smears were made on several slides and stained with Wright and Giemsa solutions. The nomenclature of the cells used here is that of Stransky and Quintos.³

The counting of the megakaryocytes was done directly on the stained smear. Several millions of the nucleated marrow cells were counted, with the correspond-

3. Stransky, E., and Quintos, F. N.: The Diagnostic Value of Examination of Sternal Marrow, *Acta med. Philippina* 2:217, 1940.

ing megakaryocytes. Then the average per million was taken. This is conveniently done under the high power objective, with the lower lens of the eyepiece divided into several portions by thinly drawn ink lines.

DESCRIPTION OF CELLS

The two interesting features associated with the present case are the atypical forms of platelets found in the peripheral blood and the superabundance of megakaryocytes in the bone marrow. These are the blood elements to be described.

Peripheral Blood.—The platelets may be grouped into three varieties. The first series consists of platelets occurring singly, or in groups and in chains of two, three or more. They correspond to the normal platelets described by Jürgens and Graupner⁴ (fig. 5 B 1). Some are old, with brilliant refractile granules, while others are a little younger.

The second variety (fig. 5 B 2) consists of big clumps of protoplasm detached from promegakaryocytes. Unless closely examined, they may be mistaken for mere clusters of mature platelets. Minute scrutiny, however, reveals that while the chromomeres are fully formed the cytoplasm has not yet fragmented itself into hyalomeres. This condition interferes with an accurate enumeration of platelets. To avoid confusion the members of the laboratory staff and I have excluded them in our respective counts. These fragments are like indiscriminately torn pieces of paper, assuming all sorts of shapes. Their structure tallies with the description of the pathologic irritative forms of platelet by Jürgens and Graupner. They are frequently found in primary polycythemia and are beautifully illustrated in figure 8 accompanying the cited article of these writers.

The third variety is composed of protoplasmic shreds broken off from old megakaryocytes. They do not show any tendency to divide into platelets. Rather, they appear to be on their way to dissolution. They stain lilac, without any trace of blue, and are studded with azurophilic granules which are much finer than, and are not disposed in heaps as, those found in the chromomeres of normal platelets. Compare figure 5 B 3 with the cytoplasm of the megakaryocyte in figure 4 B. Their similarity in structure points to a probable derivation of one from the other.

No vacuoles are found in any type.

The atypical forms observed by Downey and Nordland,⁵ and Carpenter and Flory⁶ in cases of chronic aleukemic myelosis were not encountered.

4. Jürgens, R., and Graupner, H.: Darstellung eines Entwicklungssystems der Thrombocyten, *Folia haemat.* 57:263, 1937.

Bone Marrow.—The sternal marrow is hyperplastic in all its elements. However, the megakaryocytes appear to have outpaced the leukocytes and the red blood cells. This is evident from the count of all nucleated cells, as well as from the stained smear (fig. 1.). This disproportionate megakaryopoiesis is the interesting feature for the present. All stages of development are represented and lend to a more detailed study of this blood element.

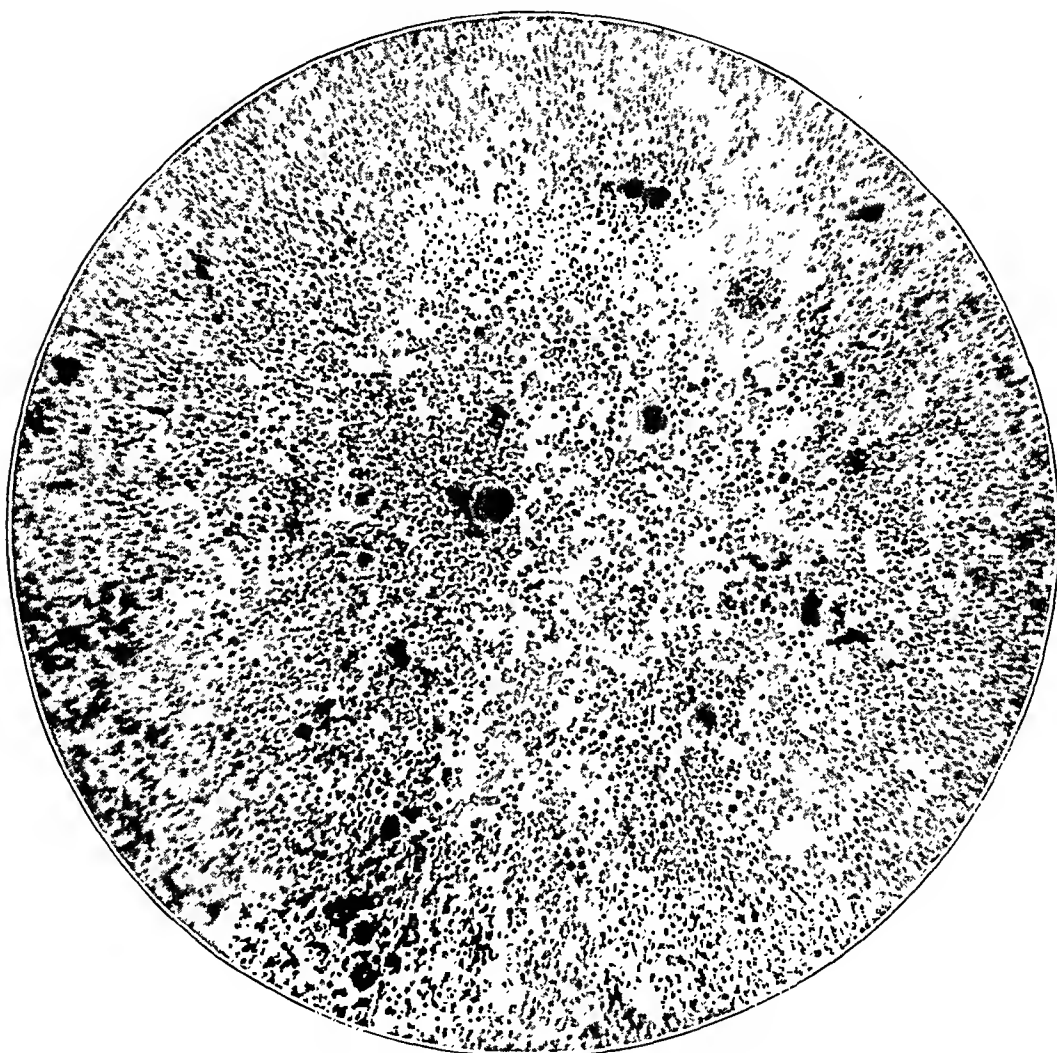


Fig. 1.—Bone-marrow smear under the low power objective, showing numerous megakaryocytes (photomicrograph by Dr. Medina-Cué).

The nomenclature, classification and criterion of maturity are still confusing. This is rather unavoidable because the nucleus and cytoplasm

5. Downey, H., and Nordland, M.: Hematologic and Histologic Study of a Case of Myeloid Megakaryocytic Hepato-Splenomegaly, *Folia haemat.* **62**:1, 1939.

6. Carpenter, G., and Flory, C. M.: Chronic Nonleukemia Myelosis, *Arch. Int. Med.* **67**:489 (March) 1941.

of the megakaryocyte do not mature concurrently as in the granulocyte. This dissociation in growth has already been observed by Barta,⁷ and it constitutes an essential difference in the maturation of this cell from maturation in other blood elements.

Hence, in selecting an adequate measure of the age of a given megakaryocyte, it is necessary to choose between the nucleus and the cytoplasm. Limarzi and Schleicher⁸ have taken "the amount, character and arrangement of azurophilic granules in the cytoplasm" as the better criterion.

The "megakaryoblast-promegakaryocyte-megakaryocyte" classification is adopted in this report since this is more universally accepted than any other.

Megakaryoblast.—This is the youngest cell of the series (fig. 2 *A, B, C, D and E*). Its contour is round or oval. The nucleus occupies a greater portion of the cell than it would in a myeloblast and is centrally located. It stains more deeply lavender than that of a myeloblast, and it stands out clearly from the cytoplasm. The chromatin threads are sharply defined, disposed in reticulate pattern and separated from one another by intervening achromatic rounded spaces. The nucleus is round (fig. 2 *E*), oval (fig. 2 *A*) or kidney-like (fig. 2 *B*), depending on the degree of maturity. No nucleoli are present.

The cytoplasm is scanty and stains a deep blue. It does not contain granules. The spongioplasm is usually more abundant in the periphery. In the very early stage it is homogeneously basophilic, and as the reaction of both nucleus and cytoplasm to the stain, as has already been observed by Medlar,⁹ is of the same degree of intensity, the contrast between them in the ordinary black and white photograph is considerably lessened, enough to make the delimitation of the nuclear margin difficult.

In the less immature forms, the spongioplasm is more abundant in the periphery than in the perinuclear zone.

Promegakaryocyte.—This stage (figs. 3 *A, B, C and D*, 4 *A*, and 5 *A*) presents the greatest number of variations in size, shape and character of both nucleus and cytoplasm. Generally the cell increases in size, the cytoplasm much more rapidly than the nucleus. The latter moves to an excentric position and becomes lobulated. The chromatin strands grow coarser and stain deeper. The interstices between strands

7. Barta, I.: Ueber Bau und Funktion der Megakaryozyten, *Folia haemat.* **47**:168, 1932.

8. Limarzi, L. R., and Schleicher, E. M.: The Reaction of Peripheral Blood and Bone Marrow in Chronic Hemorrhage and in Essential Thrombopenic Purpura, *J. A. M. A.* **114**:12 (Jan. 6) 1940.

9. Medlar, E. M.: A Study of the Megakaryocyte in the Circulating Blood of Rabbits Inoculated with Benzol and with Saponin, *Folia haemat.* **53**:397, 1935.

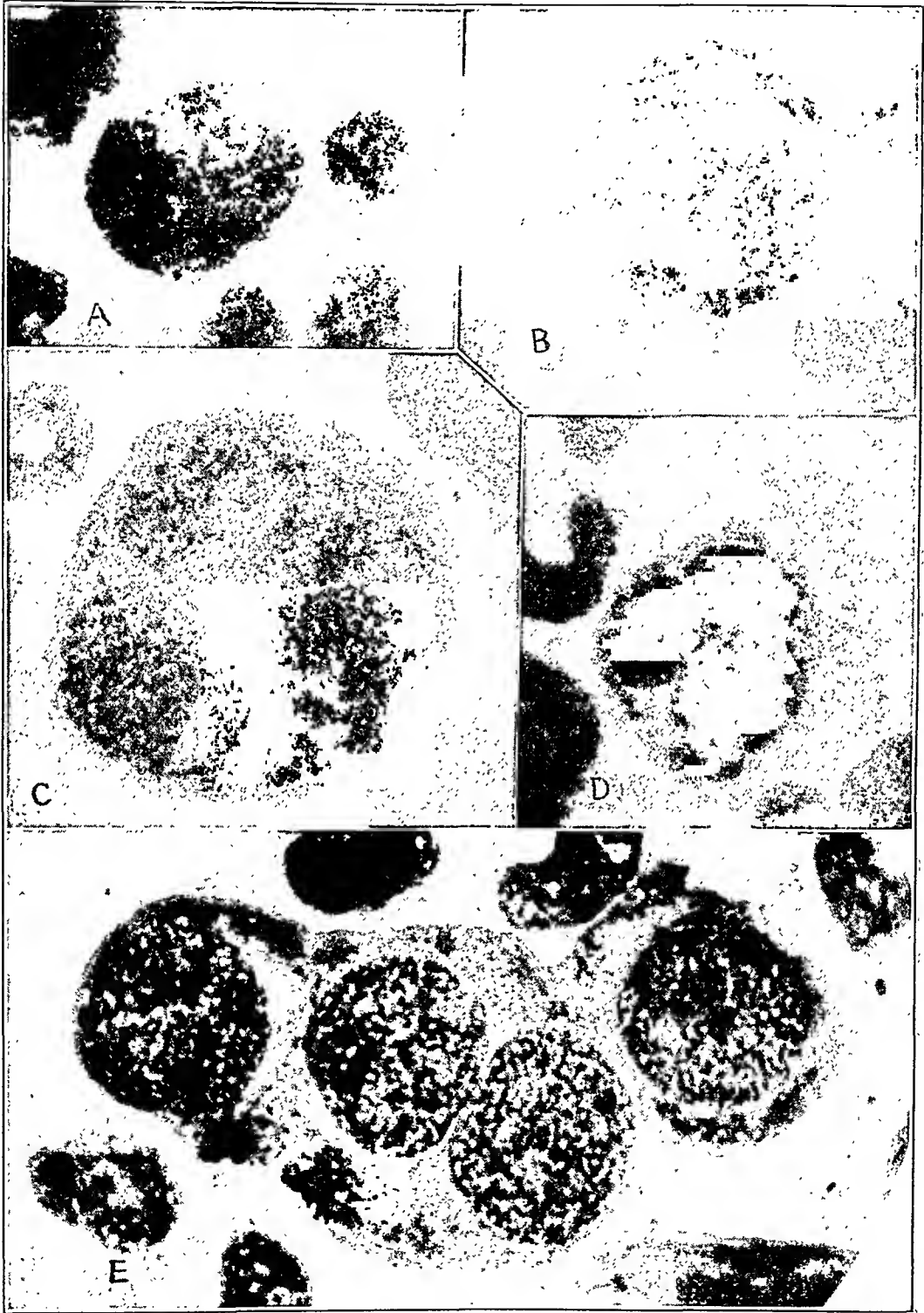


Figure 2

(See legend on opposite page)

are greatly widened. Thus, in a later stage the nucleus presents a miniature picture of a heap of noodles.

The dark blue cytoplasm becomes paler in parts as lilac refractile granules, distributed either singly or in brilliant clusters, appear near the nucleus or scattered throughout the altered cytoplasm. Pseudopodia may protrude which either are homogeneously basophilic or contain granules at the center.

The conflicting descriptions of this cell by various authors are explained by the different criteria of maturity employed.

For the sake of clearness and distinctness I have taken as the specific trait of this stage a cytoplasm that is partly basophilic and partly granular; this contrasts with the purely basophilic cytoplasm of the megakaryoblast and with the purely granular cytoplasm of the adult megakaryocyte.

The cell in fig. 3 *A*, has just emerged from the megakaryoblastic stage. The portion of the cytoplasm in the left upper quadrant has grown paler and shows granules. In fig. 3 *B*, the zone of diminishing basophilia is wider and contains more granules. In some cases, the cytoplasm presents an outer, homogeneous and an inner, granular region. As maturation progresses, the homogeneous area recedes outward till it forms a mere rim around the cell (fig. 4 *A*).

Frequently the nucleus and the adjacent granular cytoplasm are overstained (fig. 5 *A*) so that they appear as a single area, an error which gave Willi¹⁰ the impression that platelets may originate from the nucleus. Closer examination, however, reveals clearly the separation between the nucleus and the surrounding granular area. This cell offers a photographic difficulty, because it presents three different focal planes. The marginal slightly basophilic and homogenous zone is indistinctly seen in the picture; to bring it out, its outline is indicated by arrows. It sends out pseudopodia. The inner perinuclear region

10. Willi, H.: Ueber den Bau und die Funktion der Megakaryocyten und ihre Beziehungen zur thrombopenischen Purpura, *Folia haemat.* 53:426, 1935.

EXPLANATION OF PLATE.

Fig. 2.—Megakaryoblasts in different stages of amitosis. *A* (longest diameter 13.1 microns), showing at about the 11 o'clock position of the nucleus a V-shaped area with a transparent apex, the first sign of nuclear division; *B* (longest diameter 17.5 microns), a more advanced stage in which the line of cleavage and indentations of the nucleus at opposite poles are visible. The cell exhibits pseudopodia. *C* (longest diameter 23.75 microns), one nucleus (the vacuole in it is an artefact) has already separated from the mother-nucleus, while three others are being formed; *D* (longest diameter 15.25 microns), a megakaryoblast with three nuclei (slightly out of focus); *E* (longest diameter 21.35 microns), at the right, a daughter megakaryoblast is about to be separated, and at the left, the transparent zone between the two nuclei becomes basophilic preliminary to final separation (photomicrograph by Dr. A. Legarda).

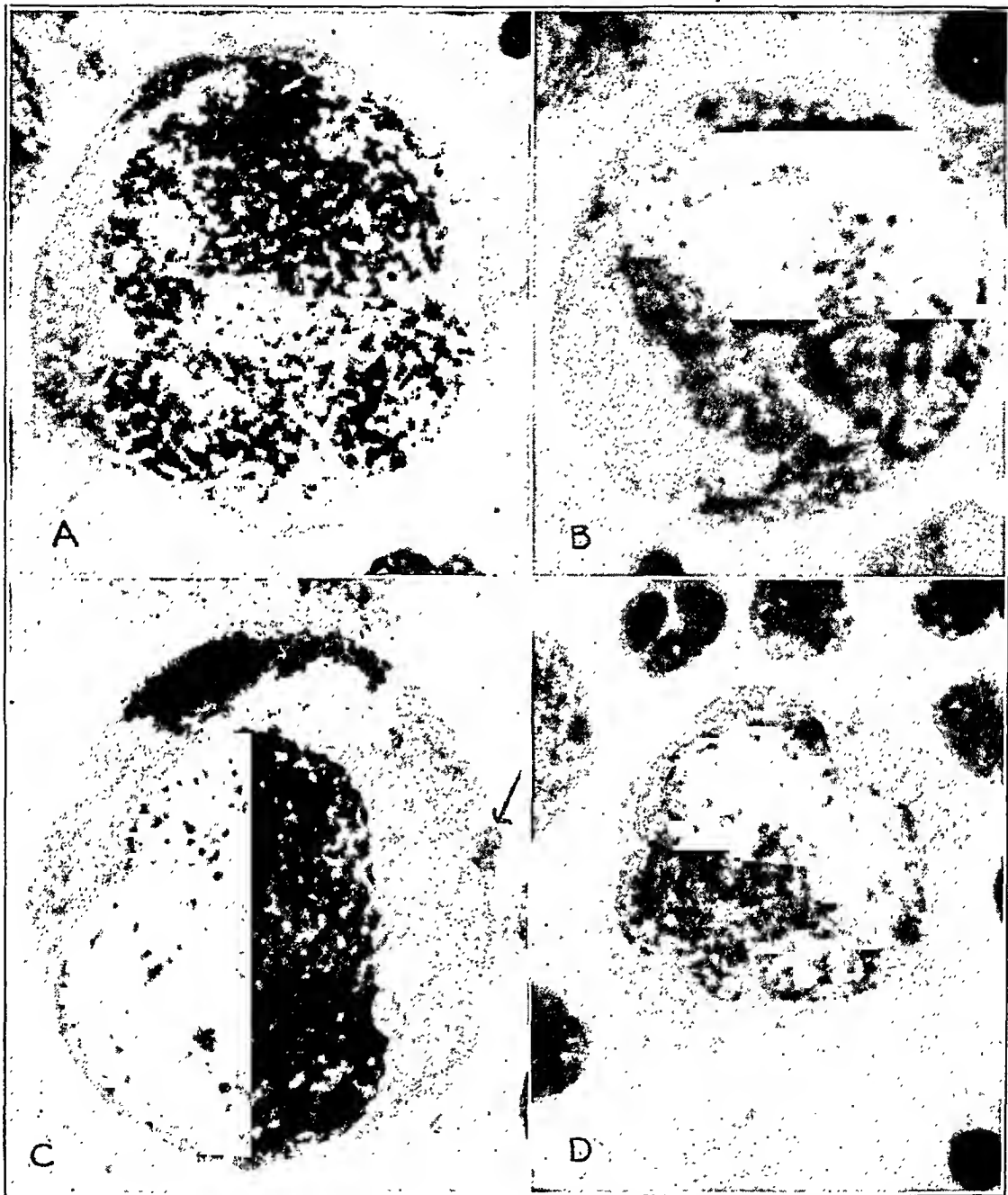


Fig. 3.—Promegakaryocytes at various stages of maturity. *A* (longest diameter 27.5 microns), cytoplasm at 10 o'clock becomes less basophilic, with clusters of granules at several places and the nucleus is indented at four points; *B* (longest diameter 25.2 microns), a more advanced stage; *C* (longest diameter 33.75 microns), darkest portion of the cytoplasm indicates basophilia, and arrow points at ingested object; *D* (longest diameter 22.5 microns), remnant of cytoplasm with mature nucleus after detachment of platelets, portions of remaining cytoplasm still basophilic and nongranular, while the rest is already forming platelets (photomicrograph by Dr. A. Legarda).

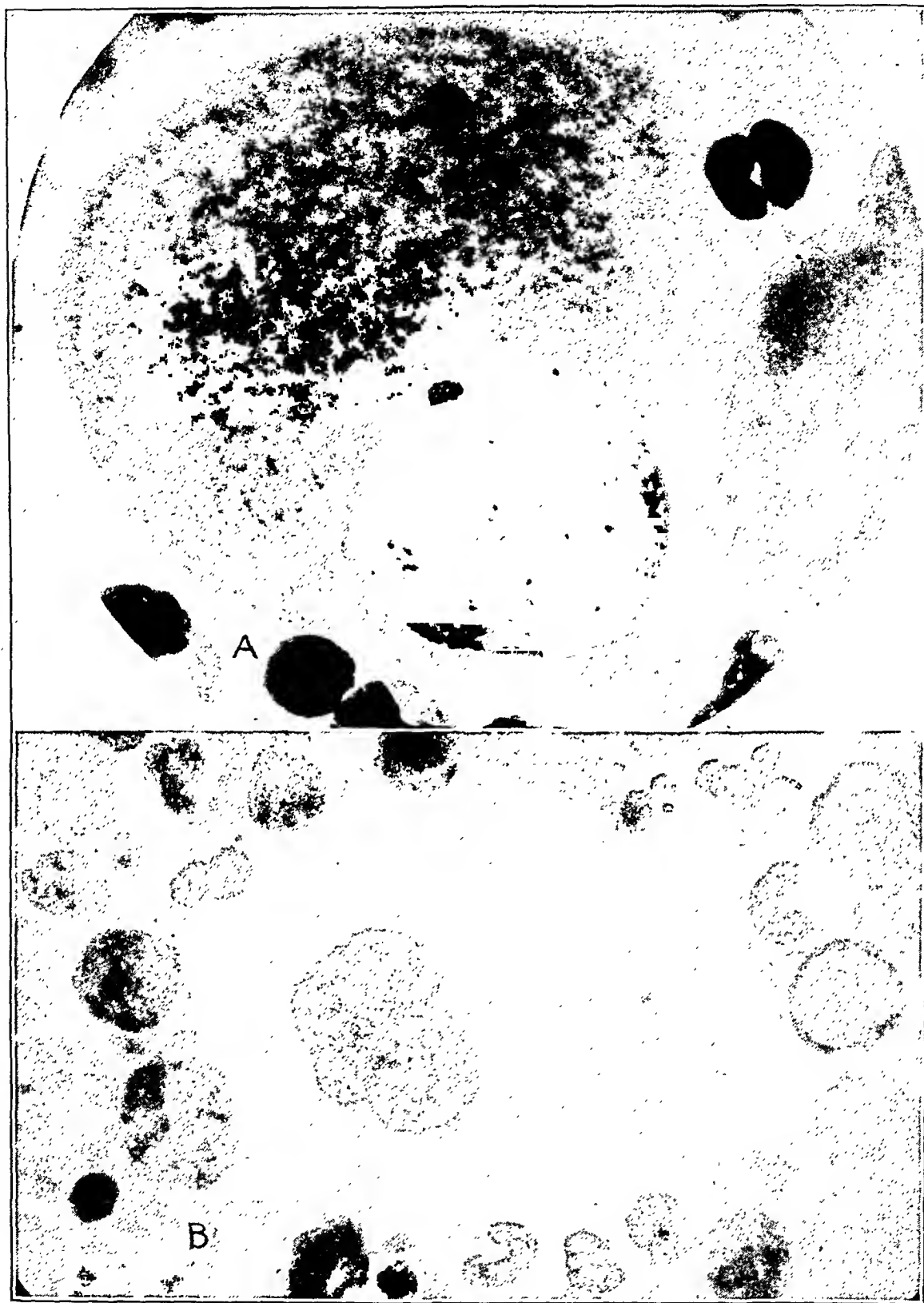


Fig. 4.—*A*, promegakaryocyte (longest diameter 43.75 microns), showing a narrow blue nongranular rim, granules of the finer type not in clusters but more or less evenly scattered and a phagocytosed body; a pearl-shaped vacuole (not a nucleolus) is at the upper part of the nucleus (photomicrograph by Dr. A. Legarda); *B*, a very mature megakaryocyte (longest diameter 69.5 microns), with transparent cytoplasm studded evenly with fine granules and containing two small pieces of ingested material (photomicrograph by Dr. Medina-Cué).

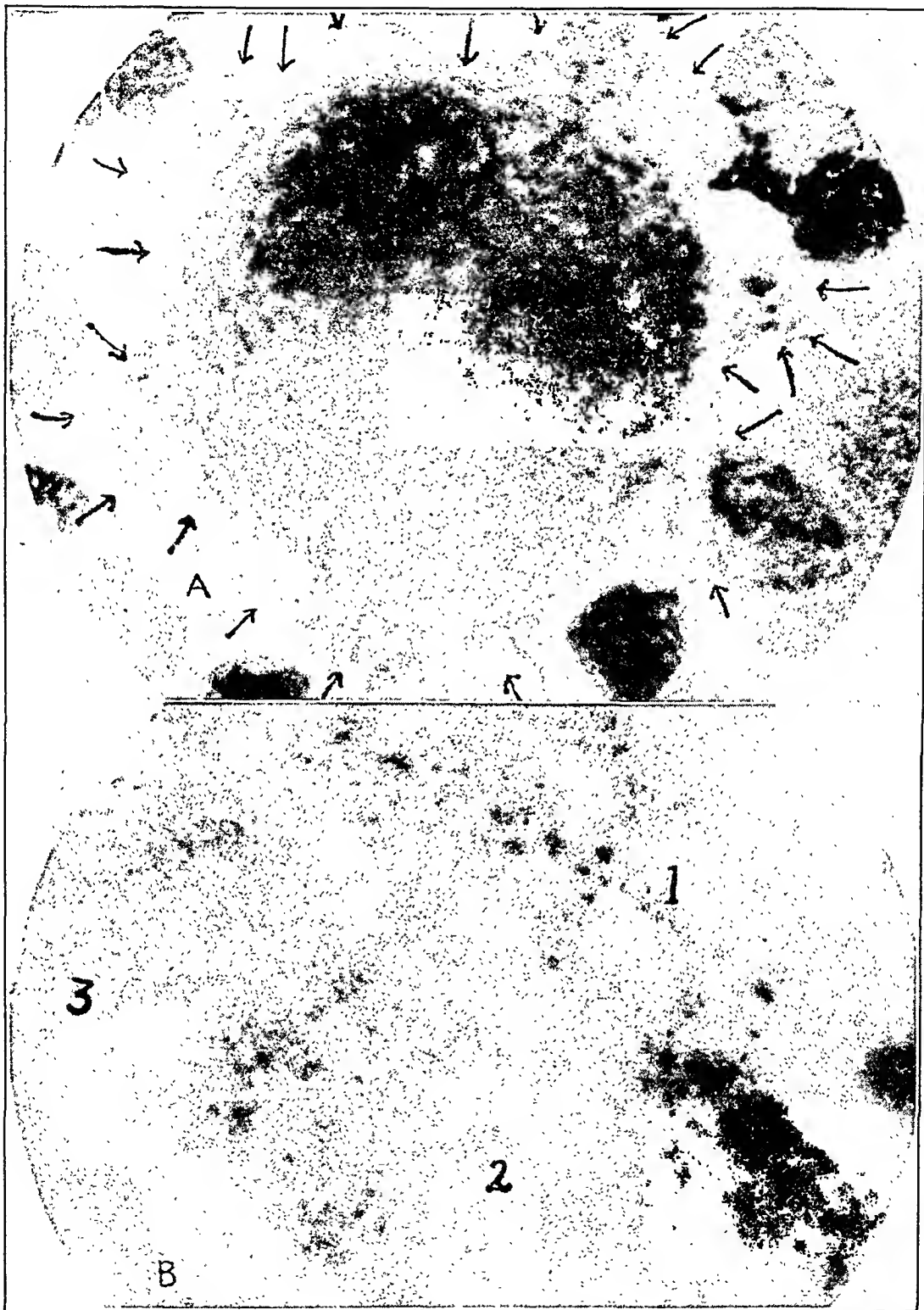


Fig. 5.—*A*, promegakaryocyte (longest diameter 43.75 microns) producing platelets; arrows indicate the wavy margin of the cytoplasm, which is divided into a peripheral slightly basophilic nongranular zone and a perinuclear granular zone; *B*, smear of peripheral blood showing three forms of platelets: (1) normal platelet, (2) pathologic irritative platelet and (3) a fragment of the cytoplasm of the kind of adult megakaryocyte shown in figure 4, *B* (photomicrograph by Dr. A. Legarda).

is a sheet of platelets in formation. The nucleus has reached its maturity, presenting a honeycombed pattern.

At times, two round or oval nuclei at opposite poles may be seen. Examples of phagocytosis and of platelet formation are observed in great number.

A promegakaryocyte may occasionally be as small as a megakaryoblast, but the nucleus is much coarser and at times is lobulated, while the cytoplasm is already well advanced in the process of fragmentation into platelets.

Adult Megakaryocyte.—This is the biggest cell of the series and marks the final stage in its development. The cytoplasm is enormous; it is uniformly granular, and it stains pale violet-pink, with or without a bluish background. The lilac granules are of two sizes. The bigger ones are arranged in clusters similar in appearance to those of the platelets; the finer ones are distributed more or less evenly throughout the cytoplasm. When granules are of the latter type, the cytoplasm loses all tinge of blue, becomes diaphanous and gradually thins out toward the periphery until one is at a loss to determine the extent of the margin and whether the dustlike particles at the outermost part are still connected with, or merely gathered around, the cell (fig. 4 B).

The lobulated nucleus recoils on itself in such a way that the opposite poles either meet or overlap one another. The chromatin materials are twined into thick threads which run in all directions, appearing like a network haphazardly woven. Oval or ellipsoid aggregates mark the crossing of the strands of chromatin.

Degenerated Forms.—This group comprises cells with torn or cytolized cytoplasm and bare or pyknotic nuclei. A percentage determination of the different types made from the first smear is as follows: megakaryoblasts (including amitotic forms) 13.5 per cent, promegakaryocytes 16.0 per cent, megakaryocytes 51.5 per cent and degenerated forms 19.0 per cent.

The pathologic forms observed by Downey and Nordland⁵ in their case of chronic nonleukemic myelosis and by Limarzi and Schleicher⁸ in thrombopenic purpura are not found in the smear.

Observations: It will be noted in the preceding description that for each type of cytoplasm there is a corresponding nucleus. However, unlike that in the granulocyte, the range of variation in character, size and shape of the cytoplasm of the megakaryocyte is much narrower and more definite than in its nucleus. For instance, the nucleus of the cell in figure 5 A has reached its maturity, but it may be found in a cytoplasm that is still immature or has already matured. This speaks for the suitability and propriety of taking the cytoplasm as the primary criterion of maturity of cells in the megakaryocytic series. Besides, the changes of the cytoplasm are more sharply defined than those

of the nucleus, thus facilitating the classification of a given cell by even a less experienced examiner.

Comment: This is a case of simple hyperplasia of the bone marrow of unknown origin, involving all the three blood elements. The granulocytes and the nucleated red blood cells increase at an equal rate, as revealed by the preservation of the normal myeloid-erythroid ratio, while the third blood element outnumbers both, as shown by the disturbance in the normal ratio between megakaryocytes and the rest of the nucleated bone marrow cells. The normal ratio, as determined by Limarzi and Schleicher,⁸ is 58.8 megakaryocytes for every 1,000,000 nucleated cells in the bone marrow.

The differential counts of both white blood cells and nucleated red blood cells are within the physiologic range.

There is no evidence of replacement of one type, or types, of cell by another in the bone marrow nor of the existence of myeloid metaplasia, since the liver and spleen are practically normal.

This hyperplasia of the central hemopoietic organ is not reflected in the peripheral blood, except in the case of the platelets, as previously noted. Abnormal cells, other than a few normoblasts, have not been observed. On the contrary, the red blood cell count and the hemoglobin content are below normal. The anemia is microcytic and hypochromic. The coagulation and bleeding times, the retractility of the clot and the icterus index are within the normal limits.

Clinically, the patient, except for an episode of fever, presents no complaints besides anemia and the symptoms and physical observations consequent on its existence.

In view of the peripheral blood picture, iron deficiency may suggest itself, but the bone marrow does not show any abnormal increase of the normoblasts or a disturbance of the myeloid-erythroid ratio in favor of the latter, which are among the usual changes in iron deficiency anemia.

A bone marrow picture of this type has not yet been mentioned in medical literature.

The history of the patient does not offer any datum which one may correlate with the origin of this obscure anemia. Only the persistence of a slight shift to the left in the peripheral blood may lead one to suspect the presence of a low grade chronic infection. It is unfortunate that no roentgenogram of the lungs was taken in view of the abnormal pulmonary conditions detected during the patient's hospitalization. However, these abnormal signs disappeared and were not found in an examination I made six months later.

Apart from this, there is nothing more that could be gathered to furnish any clue to the explanation of this case.

ORIGIN AND DEVELOPMENT OF MEGAKARYOCYTES AND PLATELETS

Besides the clinical and hematologic puzzle with which this case confounds the diagnostician and the nosologist, the numerous normal megakaryocytes present an excellent opportunity for a detailed study of their origin, development and termination.

Frey¹¹ has summarized most of what was known on this subject up to 1928; reference should be made to his article by students interested in the matter.

Several views have been propounded on the origin of the megakaryocyte. Askanazy¹² expressed the belief that it was developed from endothelial cells, leukocytes and reticular cells; Naegeli¹³ suggested the myeloblast as its probable origin and others, like Medlar,⁹ postulated the fusion of histioid elements. On the other hand, Rothermel¹⁴ concluded from her studies on the spleen of the normal cat, "that the megakaryocyte may therefore probably be interpreted as belonging to the group of cells of the erythrocyte series." In our case, Naegeli's theory is clearly borne out. In the words of Downey, Palmer and Powell,¹⁵ whose published observations are in agreement with those of Naegeli, "the nuclei . . . usually take the primary step towards differentiation by simple increase in size or by an amitotic division."

The transformation from myeloblast begins with the simultaneous occurrence of four events, namely, the appearance of a clear transparent zone in the nucleus near the margin or at any point on the destined line of cleavage, a thickening of the chromatin strands, an increase in the basophilia of the cytoplasm, and an enlargement of the cell as a whole. The cell in figure 2A shows at the left upper quadrant of its nucleus a V-shaped area (distinctly seen under the microscope) with a transparent apex. This transparent point then lengthens into a line (fig. 2B), at both ends of which the nucleus becomes indented. At the same time, the chromatin strands thicken and grow denser and the cell itself increases in size. Figure 2C shows one new nucleus which has separated from the original nucleus, while three others are in process of formation. The transparent zone,

11. Frey, H. C.: *Das Verhalten der Megakaryozyten im menschlichen Knochenmark und deren Beziehungen zum Gesamtorganismus*, Frankfurt. Ztschr. f. Path. **36**:419, 1928.

12. Askanazy, M., cited by Frey.¹¹

13. Naegeli, O.: *Blutkrankheiten und Blutdiagnostik*, ed. 4, Berlin, Julius Springer, 1923.

14. Rothermel, J. E.: A Note on the Megakaryocytes of the Normal Cat's Spleen, *Anat. Rec.* **47**:251, 1930.

15. Downey, H.; Palmer, M., and Powell, L.: The Origin of the Megakaryocytes in the Spleen and Liver in a Case of Atypical Myelosis, *Folia haemat.* **41**:55, 1930.

previously mentioned, appears to be part of the cytoplasm seen through the cleft created by the dividing nucleus. Medlar's statement that the presence of odd numbers of nuclei (fig. 2*D*) militates against the theory of Naegeli receives support only if the division is mitotic.

As soon as the new nuclei are formed, the cytoplasm adjusts its shape for the termination of the process. It lengthens, and the transparent area acquires the basophilic character of the rest of the cytoplasm. Then the latter constricts and each nucleus is furnished with its own cytoplasm. Thus a new megakaryoblast is generated.

A few important facts necessary for a clearer understanding of the physiologic and pathologic variations in the development of the megakaryocyte follow.

The nucleus of the megakaryocyte which initiates the process of multiplication retains and displays its tendency to divide in all phases of maturation. It develops so rapidly that the cytoplasm cannot keep pace with it.

The cytoplasm, on the other hand, matures in such a way as to render it fit for the performance of its functions, namely the formation of platelets and phagocytosis. This begins at the promegakaryocytic stage, i. e., as soon as basophilia diminishes and granules appear. At the same time its capacity to follow the nucleus in dividing disappears.

It seems as if there is a fundamental conflict of some sort in the purposes of the nucleus and of the cytoplasm which underlies the observed dissociation in their respective growths. The nucleus engages in the generation of as many new cells as possible before the cytoplasm commences its proper functions; the cytoplasm, on the contrary, is inactivated during the phase of nuclear activity, for as long as multiplication continues it cannot form platelets or phagocytose foreign materials.

This should not lead one rashly to conclude that amitosis, not mitosis, is normally the commoner mode of multiplication of megakaryocytes, since it adequately actualizes the nuclear tendency; an alternative hypothesis is that, mitosis being normally the commoner, amitosis is imposed on the cell by an abnormal stimulus to rapid multiplication. So far there is no evidence to establish conclusively one theory or the other. The statement of Downey, Palmer and Powell,¹⁵ "Although the occurrence of mitosis of the nuclei has been noted, this exists only in the more mature cells and is not a means of nuclear extension in the younger forms," was inferred from their observation of a case of atypical myelosis, an abnormal condition. My observation of the present case, however, tallies with theirs, for I have seen only one mitotic form in the bone marrow smear, and this is in the promegakaryocytic phase.

Now, as the megakaryoblast becomes a promegakaryocyte, the cytoplasm undergoes the alterations previously described. The emergence of granules is preceded by a diminution in the basophilia of that region in the cytoplasm where they occur. The bigger granules which are arranged in brilliant clusters are undoubtedly the precursors of the chromomeres of platelets. This area of diminishing basophilia may appear in any portion of the cytoplasm; however, it is usually first noted near the nucleus. As it widens, platelets are formed and detached, so that in the smear cells may be seen with scanty cytoplasm which is partly still basophilic and nongranular and partly forming platelets (fig. 3 *D*).

The cytoplasm which exhibits the finer and evenly distributed granules (fig. 4 *A* and *B*) is more concerned with phagocytosis than with the formation of platelets. Phagocytosed materials may be observed in the cytoplasm. At times, the same cytoplasm may be seen performing both functions, but it is not unlikely that only a few platelets will be formed, while the rest will be engaged in phagocytosis (fig. 3 *C*).

When the cytoplasm is converted into platelets it commonly does not reach the adult stage of development intact. This is the reason for not encountering frequently a fully matured megakaryocyte forming platelets. The term "fully matured megakaryocyte," as here used, designates any megakaryocyte no portion of whose cytoplasm is in a nongranular form.

On the other hand, when the cytoplasm is destined for phagocytosis, it loses entirely its basophilic character. In the stained smear, it appears purely lilac in color. The granules become finer and dustlike in size and shape and are distributed evenly. The cytoplasm itself grows more and more transparent, till it appears merely as a thin aggregate of dustlike particles (fig. 4 *B*). Finally, it disappears by dissolution, leaving the nucleus bare.

The maturation of the nucleus is characterized by the thickening of the chromatin threads, the deepening of their reaction with the stain, the widening of the interstices between them and the continued formation of lobes. In the final stage, its internal structure recalls a cross section of the mastoid bone. What distinguishes the behavior of the megakaryocytic from the granulocytic nucleus is its tendency to recoil on itself. It appears to me that such lobe formation, in contrast with the segment formation of neutrophils, is an expression of aborted amitosis. Such an impression is conveyed by comparing figures 3 *A* and *D*, 4 *B* and 5 *A*. The colored illustrations of this cell in Émile-Weil and Perlès' monograph¹⁶ on sternal puncture compared with the

16. Émile-Weil, P., and Perlès, S.: *La ponction sternale*, Paris, Masson & Cie, 1938, p. 29.

cell in figure 2 *C* seem to support this supposition. Not infrequently the nucleus succeeds in completely dividing, with the formation of multinuclear giant cells.

Much about the origin of platelets has already been said in this report. Figure 5 presents the facts more clearly than words can do. The formation of platelets seems to commence in the promegakaryocytic phase, and they may be detached and thrown into the peripheral circulation at any moment. What I designated as a third variety of platelets found in the smear of the peripheral blood is a misnomer, since in reality this "third variety" consists of torn parts of the cytoplasm of the type of megakaryocyte destined for phagocytosis.

SUMMARY

A case of a reaction of the bone marrow not previously described in medical literature is reported. This reaction consists of myeloid, erythroid and megakaryocytic hyperplasia, with preponderance of the last. It is clinically manifested by a microcytic hypochromic anemia, unrelieved by massive doses of iron. The cause is unknown.

The numerous megakaryocytes present afford an opportunity to study their character, origin and development.

A criterion for the determination of the age of a given cell, based on the cytoplasm rather than on the nucleus, is explained and justified. The behavior of the nucleus and of the cytoplasm is delineated separately with a view to explain the dissociation in their development and to establishing a suitable standpoint for the proper observation and interpretation of the different normal and abnormal variations.

The different fates of the megakaryocytic cytoplasm are discussed, one of which is the formation of platelets.

Dr. Eugen Stransky first called my attention to the uniqueness of the case and urged me to write a report of it. Dr. A. Legarda and Dr. E. Medina-Cué supplied the photomicrographs. Permission to report this case was given by the late Dr. G. Ocampo, whose staff cooperated in the preparation of this report.

OBJECTIVE AND CLINICAL STUDY OF THE TONGUE

Comparison of Normal, Desquamated and Atrophic Tongues by a Tongue Print Method

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BROOKLYN

THE REALIZATION that changes in the tongue are a consistent and reliable indication of certain deficiency states has led to many sporadic attempts to place observation of the tongue on a measurable basis. Oatway and Middleton¹ used smoked paper to make tongue prints; Kruse² utilized microscopy, and others have tried both monochromatic and color photography. Unfortunately, none of these methods have the virtue of being both simple and accurate. Moreover, none of them actually yield data which can be recorded and measured. Smoked paper prints are meritorious, except that they are negative images and the smoked paper is difficult to prepare and to transport. An added disadvantage is the need for shellacking to make permanent records. Biomicroscopy is difficult for both observer and patient. While color photography produces dramatic and striking pictures, it still does not provide an accurate record and is subject to the same optical inaccuracies encountered in monochromatic photography, namely, failure to record faithfully changes in surface contour.

This contribution is made in an effort to devise a simple, cheap and accurate method of recording surface changes in the tongue. It is further intended to describe the variations encountered in the normal tongue and, finally, to demonstrate the uses of this method in certain clinical entities.

METHODS

An inking solution is made by heating at boiling temperature for ten minutes in a water bath 2 Gm. of Evan's blue and 10 Gm. of gum acacia in 40 cc. of distilled water. When the solution is cool, a few drops of chlorobutanol may be added to prevent the growth of molds. This solution will be the consistency of thick cream, odorless, tasteless and nonpoisonous. It has excellent spreading and printing qualities. Moreover, it dries rapidly and is permanent.

Printing paper should be heavy bond and should be well glazed at least on one surface. Kymograph paper serves the purpose admirably. It is cut up in

From the Department of Medicine of the Long Island College of Medicine and the Kings County and Long Island College Hospitals.

1. Oatway, W. H., Jr., and Middleton, W. S.: Correlation of Lingual Changes with Clinical Data, *Arch. Int. Med.* **49**:860 (May) 1932.

2. Kruse, H. D.: The Lingual Manifestations of Aniacinosis, with Special Consideration of the Detection of Early Changes by Biomicroscopy, *Milbank Mem. Fund Quart.* **20**:262, 1942.

oblong strips 12 by 16 cm. and clipped to a backing of stiff cardboard. A supply of this paper, the inking solution and a number of sterile 4 by 4 in. (10 by 10 cm.) gauze pads are all the materials needed to make observations.

In practice, the patient is asked to protrude his tongue in a relaxed state with his mouth slightly open. He is warned not to retract it until told to do so. Some difficulty is encountered in patients who contract their tongue when protruding it, but a demonstration by the observer will in most cases solve this problem. Prints of the tongue protruded in a contracted state are not accurate, and this error must be carefully avoided. Also, it is desirable to protrude the tongue only about 1 inch (2.5 cm.) from the margin of the teeth, as most persons cannot protrude it farther than this in the relaxed state. The tongue is then dried thoroughly with the sterile gauze. A generous amount of the inking solution is applied with another piece of sterile gauze. The solution should be well worked over the distal third of the tongue, including the tip and as much of the mar-

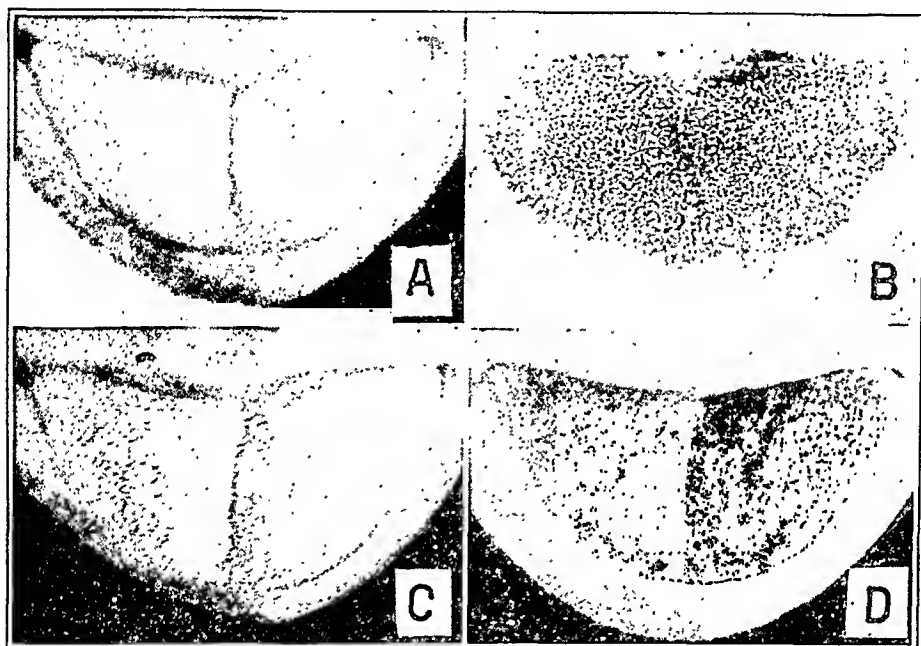


Fig. 1.—Photographs, taken under different conditions, of a normal tongue of the filiform, slightly fissured type compared with its print. In *A* the tongue has saliva on it, while in *C* it has been dried. When the inking solution is applied, the appearance is as in *D*. Note in the print, *B*, that the mucous membrane of the tongue is thrown up into folds; every detail is recorded faithfully, including the papillae and the folds and creases.

gins as possible. The excess ink is then blotted off with a third piece of gauze. By gently but evenly pressing the backed paper against the tongue, three or four successive prints may be made. This must be done rapidly, for the ink dries on the tongue in a few seconds. One of the prints made will generally be satisfactory, showing great detail. If none is acceptable the whole process must be repeated from the start because satisfactory printing depends on having just the right amount of ink of the proper consistency on the tongue. This knack is the secret of the whole process, but, fortunately, it is easily learned with practice.

With some patients, difficulty will be encountered from excessive salivation. This leads to dilution of the ink and blurring of the print. It is easily avoided

by placing dentist's rolls in the patient's mouth on each side over the opening of the salivary ducts beneath the tongue.

RESULTS

Interpretation of Tongue Prints.—An average normal tongue print is shown in figure 1 *B*. The detail is great and withstands scrutiny with a hand lens. The photograph of the same tongue (fig. 1 *A*) with saliva on it shows little detail; in fact, one might suspect it to be a so-called smooth tongue. A better picture is obtained when the tongue is dried, (fig. 1 *C*) but this still does not permit accurate study. When the inking solution is applied as in figure 1 *D*, a further detail is noted in the photograph: namely, the mucous membrane of the normal tongue is often thrown up in folds and resembles a mulberry. This produces small fissures on the surface. Not all tongues have this feature, as will be shown subsequently, but it is notable that such small fissures are recorded faithfully in the print, whereas they are

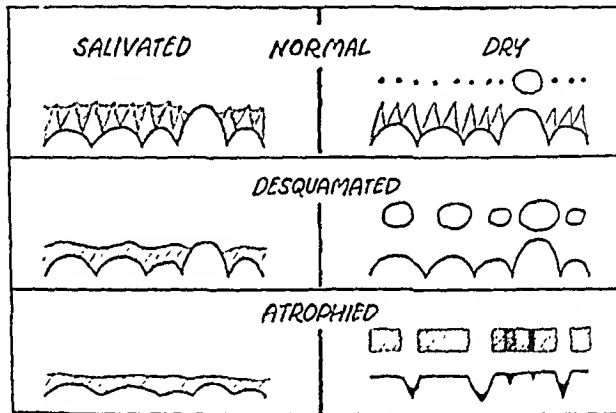


Fig. 2.—Schematic representation of the surface of the tongue showing why it appears smoother when salivated. A projection of the cross sections shows how the papillae and fissures will print.

difficult to discern in the photograph. The obvious conclusion to be drawn is that simple direct printing of the tongue by the method described is more useful than photographing it.

In order to understand the detail in the prints, it is necessary to be cognizant of both the surface anatomy of the tongue and the mechanics of the printing which registers these structures. Fortunately, only three features of the surface of the tongue enter into the problem. These are the filiform papillae, the fungiform papillae and the underlying folds, fissures or creases in the mucous membrane. With this method only the distal third of the tongue can be conveniently studied; hence the structures present on the proximal two thirds of the tongue are not included. With a little imagination, and by reference to figure 2, it will be easily perceived how these structures will print. The filiform papillae, which are small cornified tufts of epithelium

with two or three points to them, will pick up a minute drop of ink and print as either a round or, more frequently, a star-shaped dot. On the other hand, the fungiform papillae, which are larger and smooth, pick up little ink. Because the ink dries rapidly, the domed surface will not print at all, and only the sloped sides, which retain a little ink in the crevices, will print. As a result, fungiform papillae come out in the print as round "cheese holes." Figure 3 *C* shows typical filiform papillae magnified twelve times, while figure 3 *D* shows a

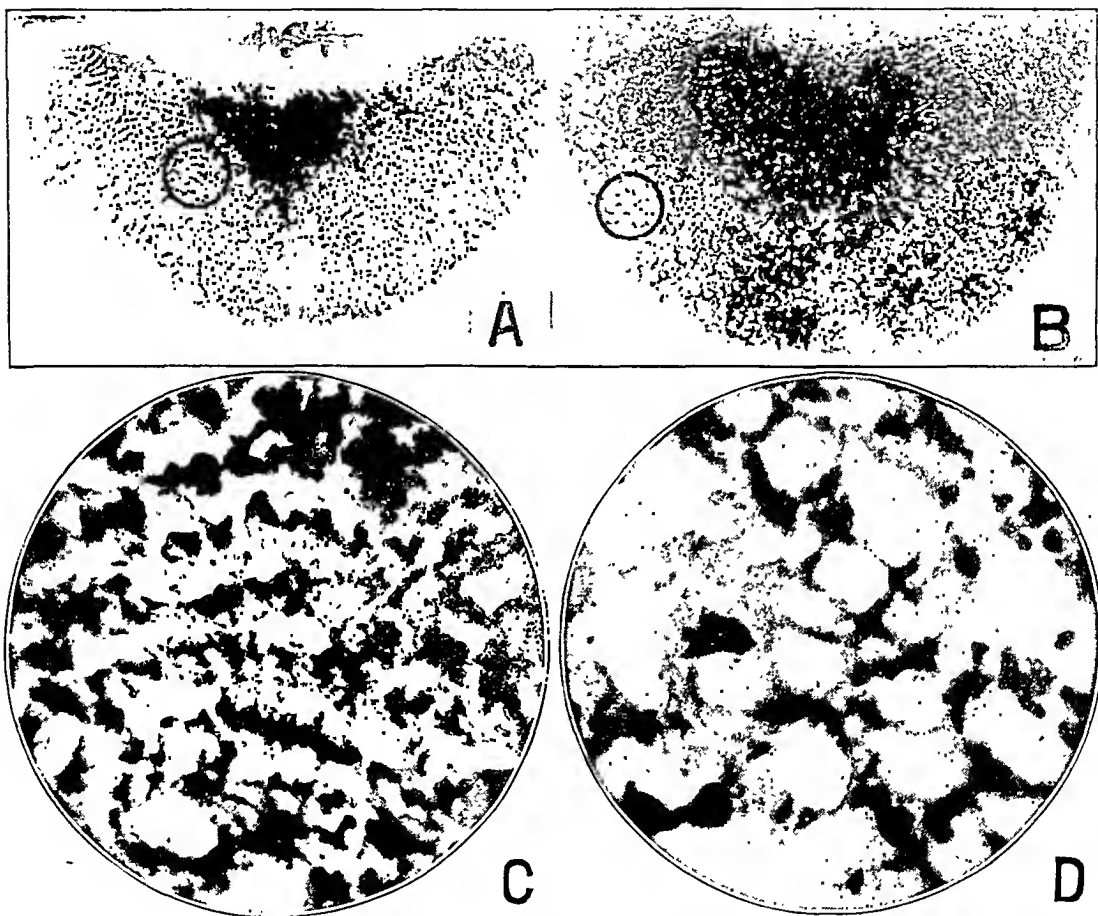


Fig. 3.—Two types of normal tongues: *A*, linear and *B*, fungiform. Enlargements ($\times 12$) of the surface structure; *C*, detail of filiform papillae and their linear arrangement; *D*, detail of a group of fungiform papillae.

group of fungiform papillae at the same magnification. When the tongue atrophies, the surface flattens and papillary structure disappears; it may be expected to print as a monotone, interrupted only by dark lines of smaller fissures and larger linear blanks of the deeper fissures, which are not filled with ink and thus do not print (figs. 2 and 4).

Enumeration of the Papillae.—By study of a group of 99 healthy men who were medical students in the third decade of life and who

were theoretically on adequate diets, certain features and variations of the normal tongue could be defined. First of all, an attempt was made to enumerate the number of fungiform and filiform papillae seen on the prints. It would be too tedious, if not impossible, to count all the papillae obtained in each print. Instead, the counting was restricted to circles exactly 0.5 cm. in diameter which were drawn with india ink on the tongue prints. The center of the circle for enumeration of the filiform papillae was always placed at a point 1 cm. from the

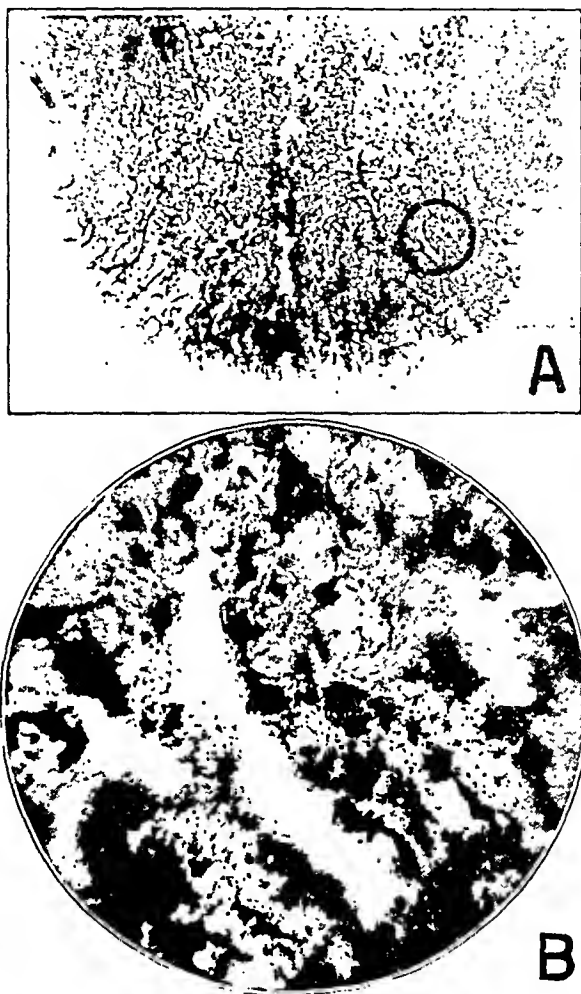


Fig. 4.—*A*, the print and *B*, the enlargement ($\times 12$) of the atrophic tongue of patient J. J. (see table 3). Note the sharp creases and grooves of the surface, with complete absence of papillary structure.

midline and 1 cm. from the tip of the tongue, as measured on the tongue print. This was usually a particularly advantageous area, since the filiform papillae were not too crowded, as they were nearer the center of the tongue, yet they were not sparse as they were on the tip and margins. The centers of the circles for the enumeration of the fungiform papillae were always placed on the margins of the tongue.

Usually, three areas were selected which demonstrated the fungiform papillae well, and the results were averaged for a particular tongue.

The results of a papillae count made by this method are summarized in table 1. The average count of filiform papillae on the tongue prints of the entire group was 52.2, and the average count of fungiform papillae was 8.1. The data further show that there is a wide spread from the mean for both types of papillae, while the standard deviation is the high for both. This indicates that there is only a limited usefulness to enumeration of the papillae, since there does not seem to be, judging from the data obtained, a critical level for the number of papillae of the normal tongue. However, this does not obviate its practicability when prints of the same tongue are observed over a period of time or when abnormal tongues are studied, as will be shown subsequently. It must also be pointed out that the counts, particularly for the filiform papillae, may not correspond to a direct anatomic count of the same area. That is, a filiform papilla may print as two distinct dots if it has a bicornate head, whereas it is in reality only one papilla.

TABLE 1.—*Papillae Counts of Normal Tongues*

Papillae	Average	Highest Number	Lowest Number	Standard Deviation
Filiform.....	52.20	81	34	10.74
Fungiform.....	8.10	23	3	3.89

Average of counts of papillae on tongue prints of 99 men in the third decade of life (average age 21). Counts are for a circle 0.5 cm. diameter; area 0.196 cc. Center of circle for the filiform papillae count is 1 cm. from tip and 1 cm. from the middle of the tongue. Counts of the fungiform papillae are average counts from 3 similar circles on the margins of tongue.

Types of Tongues.—Comparison of the tongue prints shows that no two tongues are alike. However, there are certain characteristic features which permit grouping the tongues in types. Thus, the tongue in figure 1 *B* shows predominance of the filiform papillae and, as a secondary feature, is slightly fissured. Figure 3 *A* portrays a tongue whose only dominant feature is a linear arrangement of the filiform papillae, while in figure 3 *B* the prominent feature of the tongue is a large number of hypertrophied fungiform papillae scattered over the surface. The normal fissured tongue is shown in figure 5 *D*. A small group of the tongues have slight fissuring as their only dominant feature (not illustrated). The types of tongues observed in 99 medical students are classified in table 2. Approximately two thirds of the group had tongues which showed only one dominant feature, and of these the commonest by far was the filiform type. With the exception of the fungiform type, the others were relatively uncommon. The other third of the group had tongues with a dominant and also a secondary feature. Again in table 2, it may be seen that the filiform, slightly fissured

type was the commonest while the fungiform linear type was next in order of frequency.

The value of such a classification is that it makes available a measuring stick for testing the normalcy of a particular tongue by mere inspec-

TABLE 2.—*Types of Normal Tongues*

Tongues With One Dominant Feature	Number	Tongues With a Dominant Feature Plus a Secondary Feature	Number	Total
Filiform.....	38	Filiform, slightly fissured.....	12	50
Fungiform.....	15	Fungiform, linear.....	9	24
Fissured slightly.....	6	Slightly fissured, filiform.....	5	11
Fissured.....	5	Fissured, fungiform.....	4	9
Linear.....	3	Linear, fungiform.....	2	5
Total.....	67	32	99

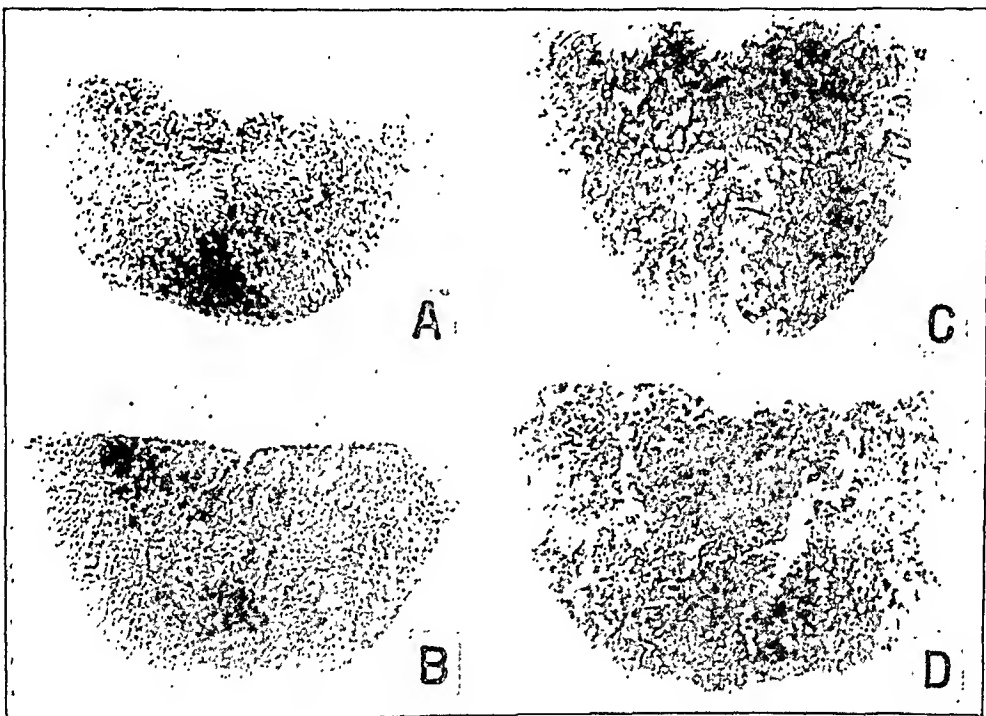


Fig. 5.—Prints illustrating various types of folds and creases of normal and of abnormal tongues. *A* and *B*, tongues of patients with cardiac disease and nephritis, respectively. Both tongues were edematous. Note the horizontal serrations, especially at the margins; the filiform papillae do not print clearly because they are swollen as a result of the edema. *C*, print of the atrophic fissured tongue of a 90 year old avitaminotic patient; *D*, print of the normal, fissured tongue of a medical student. Note that in *D* papillary structure is normal, while in *C* it is completely absent.

tion of the tongue print. In order for a tongue to be classed as normal, it must fit into one of the types specified. Since 50 per cent of normal tongues are of the filiform type, the chances are good that if a tongue in question is of the filiform type it is normal. On the other hand, if a particular tongue is fissured slightly, or even decidedly, it does not

of necessity mean that it is abnormal, since 20 per cent of the tongues which are normal are fissured. The same reasoning applies to prominence of the fungiform papillae, but in this case, as is shown later, only when the filiform papillae are intact.

Features of the Abnormal Tongue.—By study of the prints of the tongues of over 100 patients with definite histories of dietary deficiencies of long standing, the features of the abnormal tongue were elucidated.

TABLE 3.—*Abnormal Features of Tongue Observed in Fifteen Patients with Definite Histories of Dietary Deficiencies*

Name	Age	Sex	Clinical Diagnosis	Filiform Papillae Count	Fungiform Papillae Count	Abnormal Feature of Tongue Shown on Prints	Clinical Appearance of Tongue
J. J.	65	M	Pellagra	7	13	Longitudinal ridging	Smooth, magenta
F. M.	49	M	Chronic alcoholism, avitaminosis	28	6	Longitudinal ridging, cross- hatching	Normal
T. C.	59	M	Diaceylmorphine addict, avitaminosis	23	19	Crosshatching	Normal
A. W.	91	F	Senility, avita- minosis	0	9	Absence of fili- form and fungi- form papillae	Fissured, raw, red
M. L.	80	F	Arteriosclerosis, avitaminosis	0	7	Crosshatching	Smooth, atrophic
S. L.	65	F	Plummer-Vinson syndrome	3	14	Crosshatching	Smooth, atrophic
H. A.	59	M	Chronic alcoholism, avitaminosis	0	8	Crosshatching	Smooth, magenta
L. B.	71	F	Achlorhydric anemia, avitaminosis	0	17	Crosshatching	Smooth
E. A.	39	M	Chronic alcoholism, cirrhosis of liver	8	7	Crosshatching	Questionably smooth
E. L.	50	M	Peptic ulcer, avitaminosis	18	21	Crosshatching	Smooth
A. K.	44	M	Chronic alcoholism, avitaminosis	3	12	Longitudinal ridging	Smooth, red
A. M.	28	M	Lobar pneumonia, avitaminosis	0	10	Crosshatching	Smooth, red
W. J.	65	M	Beriberi heart (?), avitaminosis	20	19	Crosshatching	Normal
W. C.	40	M	Chronic alcoholism, cirrhosis of liver	0	18	Crosshatching	Smooth
L. S.	64	M	Chronic alcoholism, avitaminosis	5	11	Crosshatching, longitudinal ridging	Smooth, red
Average.....				7.7	12.7		

In table 3 are summarized the detailed observations on 15 of these patients selected at random. The striking feature is a pronounced decrease in the number of filiform papillae and a slight increase in the number of fungiform papillae. Thus, the average count of filiform papillae for this group was 7.7, compared with an average count of 52.2 for the normal (table 1); for the fungiform papillae, the average count was 12.7 compared to 8.1 for the normal. Expressed differently, there is in the abnormal tongue a reversal of the normal ratio of filiform to fungiform papillae.

The tongue prints of a group of 7 patients with proved pernicious anemia showed essentially the same changes in the papillae counts. It is noteworthy that after treatment in this group, the papillae counts reverted toward the normal levels (see table 4). Two other features were discovered to be consistently present in the abnormal tongues. One was the appearance of a crosshatched pattern in the print. This is as a rule better seen in heavy prints than in lighter ones (fig. 6). After therapy, this sign has a tendency to disappear. We interpret this to signify a thinning of the mucous membrane of the tongue, so that the impression of the underlying lattice work of fibromuscular structure prints through. Ordinarily the mucous membrane is too thick, particularly when the filiform papillae are intact, for these inner

TABLE 4.—*Abnormal Features of Tongue Observed in Seven Patients with Proved Pernicious Anemia*

Name	Age	Sex	Papillae Count Before Treatment		Papillae Count After Treatment		Abnormal Feature of Tongue Shown on Prints	Clinical Appearance of Tongue
			Fili- form	Fungi- form	Fili- form	Fungi- form		
D. V.	61	F	12	2	20	10	Decided longitudinal ridging	Normal
A. B.	59	F	0	14	26	16	Decided longitudinal ridging	Smooth
E. G.	70	F	6	5	11	10	Longitudinal ridg- ing, crosshatching	Smooth
H. B.	57	F	9	15	22	10	Decided longitudinal ridging	Normal
F. K.	54	M	24	9	32	11	Crosshatching	Smooth at edges
S. S.	42	M	0	33	32	11	Crosshatching	Smooth, bald, red
M. W.	79	F	0	10	12	8	Crosshatching	Smooth, red
Average.....			7.3	12.5	22.5	10.4		

structures to print. This crosshatch feature of the print presumably is similar to the horizontal serrations seen grossly on the margins of the tongues of persons suffering from dietary deficiencies. At any rate the crosshatched pattern can be taken as a reliable indication that thinning of the mucous membrane of the tongue has taken place. It has been seen in prints of normal tongues only, under conditions leading to increases in hydration, such as exist in patients with cardiac and nephrotic edema (fig. 5 *A* and *B*). As can be seen in tables 3 and 4, it is present in nearly all the prints of the tongues of persons with dietary deficiencies and in 4 prints of the tongues of patients with pernicious anemia.

The other significant feature of abnormal tongues is longitudinal ridging (fig. 7 *A*). In this condition the mucous membrane is thrown up into folds resembling ridges along the longitudinal axis of the tongue. The reason for this may be a diminution in the inner muscular volume of the tongue, which throws the mucous membrane into folds, just as

the skin of an apple wrinkles when it dries. It occurs along the longitudinal axis because the tongue is weaker structurally in its horizontal axis. As additional evidence, it may be pointed out that the tongue of the patient who is dehydrated frequently shows the same feature even on gross inspection. However, in some cases an element of hyperplasia of the mucous membrane may play a part. Others have called this abnormal feature a "scrotal pattern" of the tongue, but we believe the term "longitudinal ridging" to be more accurate and descriptive, though perhaps less colorful.

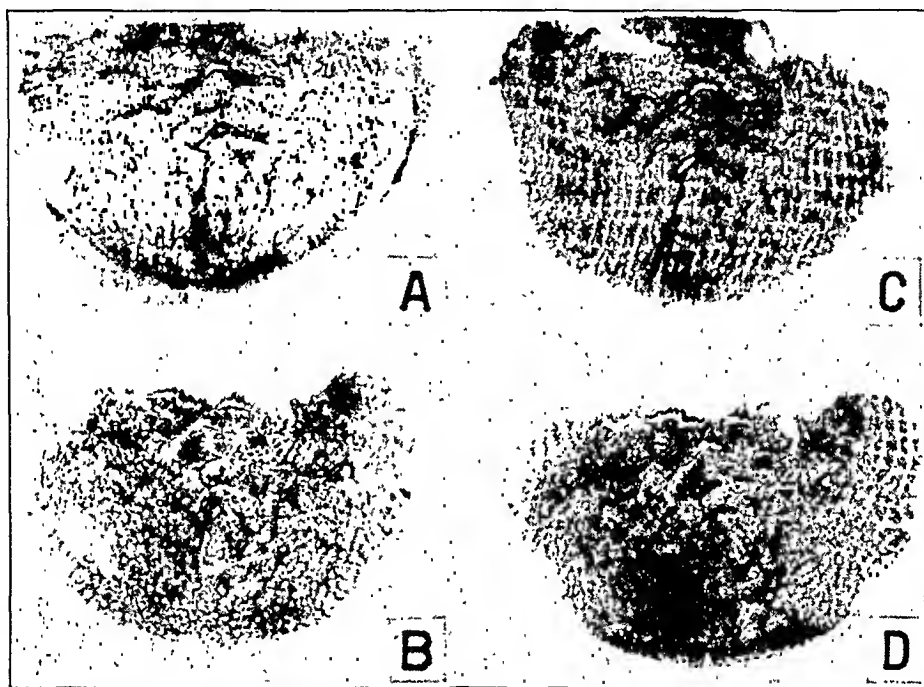


Fig. 6.—Prints of tongue before and after treatment of patient A. M. (table 3), with lobar pneumonia and acute avitaminosis. *A*, the tongue before treatment; complete absence of filiform papillae while groups of normal fungiform papillae remain, producing a desquamated appearance. *B*, appearance decidedly changed after a week's treatment for the patient's disease with nicotinic acid and riboflavin; considerable growth of filiform papillae, while the fungiform papillae have hypertrophied. *C* and *D*, heavier prints taken at the same time as *A* and *B*, respectively. This was done to bring out the crosshatched pattern, which is a distinctive sign of thinning of the mucous membrane.

In tables 3 and 4 it may be seen that longitudinal ridging is much less common than crosshatching. This is because longitudinal ridging is an evanescent sign, and may be present only for a few hours to one or two days. Thus in the case of D. V. (fig. 7 and table 4) the ridging disappeared in three days, after only two injections of extract of liver. Noteworthy is the fact that when ridging is pronounced, crosshatching does not appear in the print.

It may also be shown by study of tables 3 and 4 that there is no distinct separation in type between the tongue of a patient suffering from dietary deficiencies and that of one with pernicious anemia. It appears probable that the same element is deficient in each of the 2 patients. In this we concur with Sevringhaus and Kyhos.³ Incidentally, all our patients with pernicious anemia received adequate daily doses of riboflavin and nicotinamide as part of their treatment.

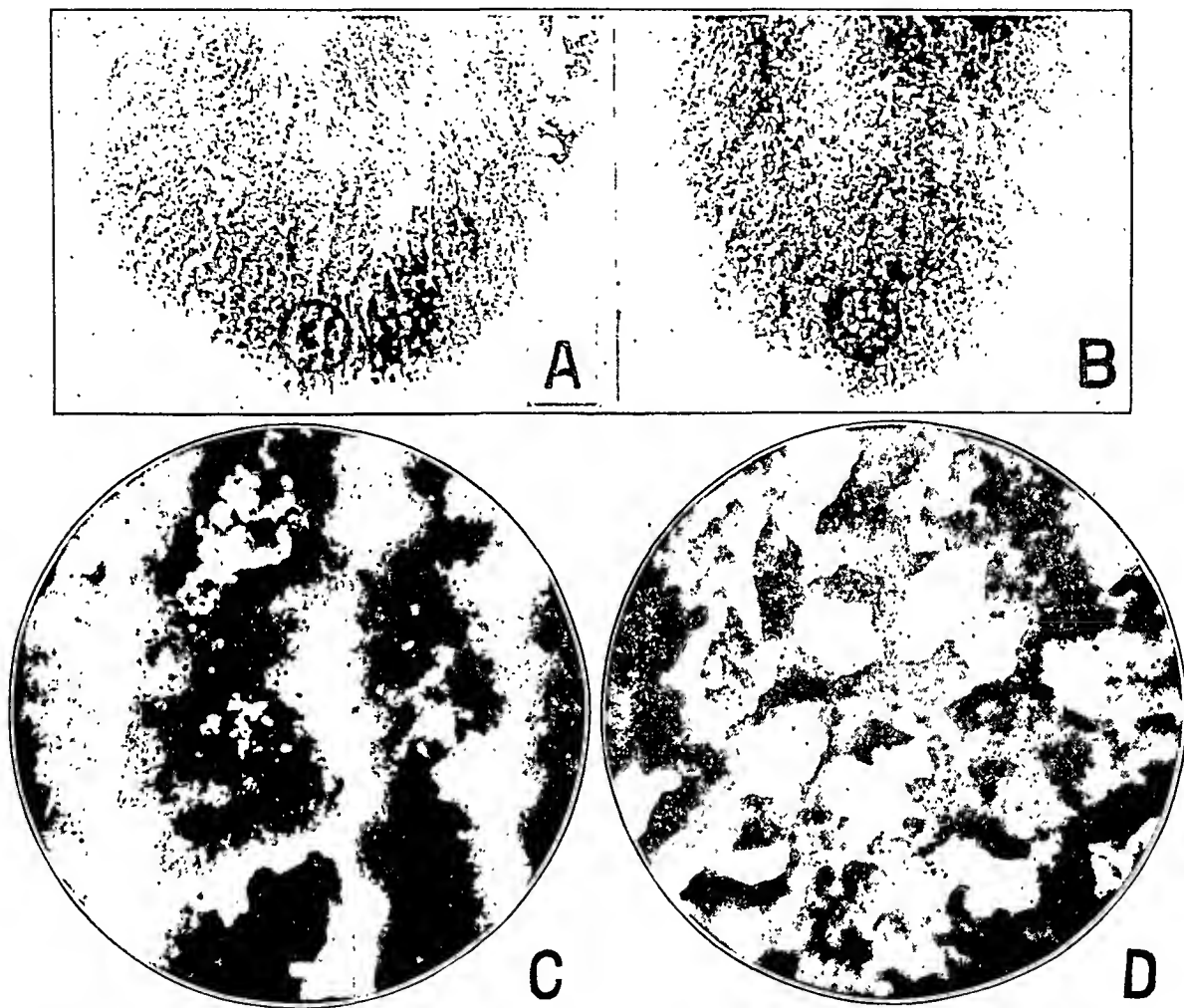


Fig. 7.—Prints (*A* and *B*) and enlargements (*C* and *D*) of the tongue before and after a patient with pernicious anemia was given treatment with extract of liver and with nicotinic acid and riboflavin (see D. V., table 4). *A* and *C*, before treatment; note the longitudinal ridging. *B*, three days later; the ridging has disappeared. The enlargement, *D*, now shows rudimentary hypertrophied fungiform papillary structure.

COMMENT

The plethora of terms descriptive of types of tongues in the medical literature is confusing. Many writers have described a certain type as distinctive of a particular clinical entity. However, it is easier to

3. Sevringhaus, E. L., and Kyhos, E. D.: Reversal of Lingual Atrophic Changes with Nicotinamide Therapy, *Arch. Int. Med.* **76**:31 (July) 1945.

read the description than it is to pick out such tongues in the ward. What is needed is a classification of the abnormal tongues based on the fundamental mechanism of the pathologic changes. Since the crucial structures on the lingual surface are the papillae, any attempt to define changes in the tongue should be based on them. In figure 8, a chart which aims to clarify the lingual changes encountered in disease, the normal tongue is defined as one with its filiform and fungiform papillae intact both as to number and as to structure. In disease the first tendency is for the tongue to desquamate; that is, the cornified filiform papillae dissolve or wear off from the surface of the tongue. In this stage the tongue is frequently coated. Once desquamated, the tongue lacks protection and is apt to become inflamed, red or swollen. If recovery takes place, the papillae revert to normal; if not, the tongue goes on to atrophy, which is defined as the absence of all filiform papillae and a decided diminution of fungiform papillary structure. Once in this stage the tongue of a patient shows little tendency toward

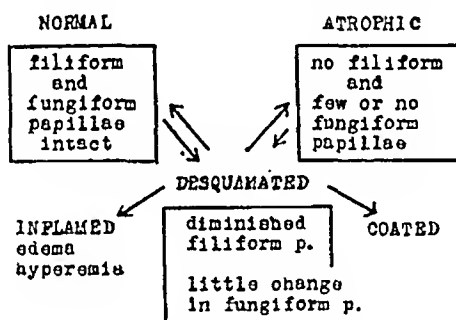


Fig. 8.—Mechanism of the changes causing the abnormal tongue.

recovery even with treatment. In figure 9 *B* is shown the atrophic tongue of an avitaminotic patient 80 years old, with complete absence of papillae. Treatment for three months with large doses of nicotinamide and riboflavin failed to bring about any changes in the tongue (fig. 9 *D*). The tongue of a patient with Plummer-Vinson syndrome (hypochromic anemia) on the other hand, showed some remains of fungiform papillary structure before treatment (fig. 9 *A*). After one month of therapy with iron, thiamine, riboflavin and nicotinamide there was considerable growth of filiform papillae (fig. 9 *C*).

This classification recognizes the fact, often forgotten, that the fungiform papillary structure is the underlying unit of the tongue. It is from the sides of the fungiform papillae that the filiform papillae grow.⁴ Hence, even if the filiform papillae disappear, the fungiform papillae should remain. This is exactly what enumeration of the papillae of

4. Smith, P. E.; Copenhaver, W. M.; Severinghaus, A. E., and Goss, C. M.: *Bailey's Text-Book of Histology*, ed. 11, Baltimore, William Wood & Company, 1944.

normal and abnormal tongues by the print method has demonstrated. Finally, if the tongue is atrophic both types of papillae should disappear, and again proof of that fact can be obtained in serial prints of the tongue which does not respond to therapy.

Therefore, a plea is made to workers in this field to restrict themselves to terms here outlined. Only then can it be discovered whether several factors lead to the development of an abnormal tongue or whether one factor alone is involved. Moreover, the degree of dietary deficiency required to bring about first desquamation and then atrophy of the tongue can be clearly defined, and the response to therapy accurately gaged.

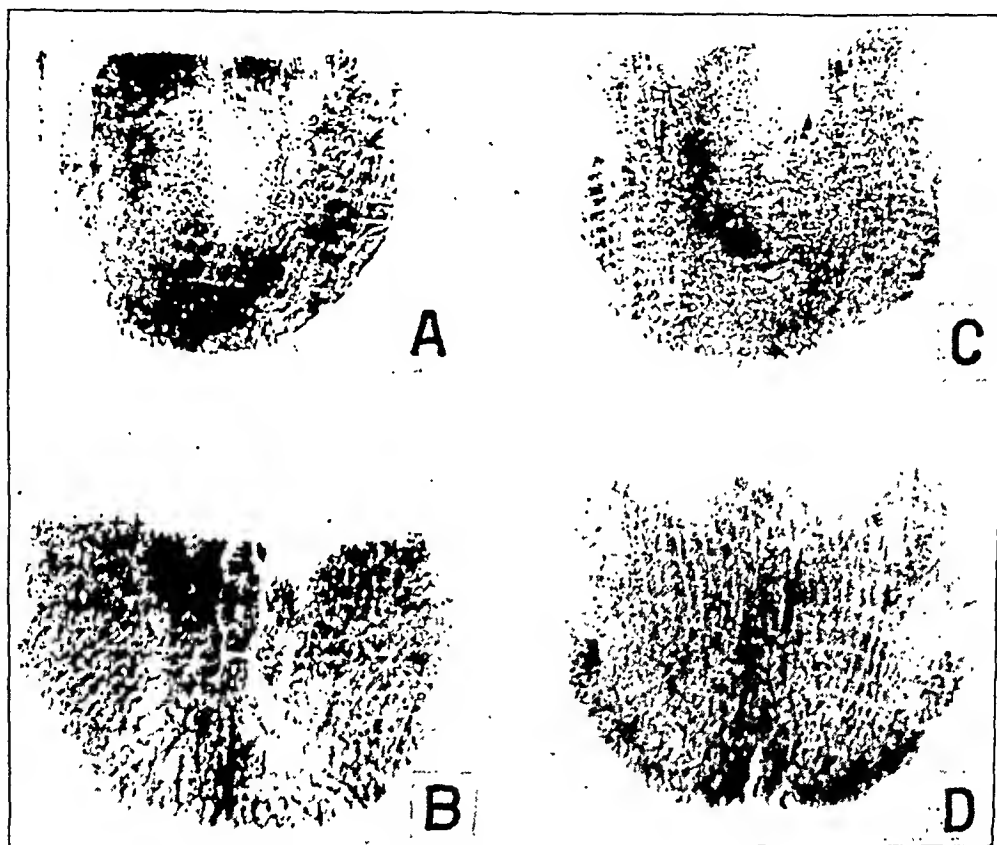


Fig. 9.—Prints selected to demonstrate the difference between the desquamated and the atrophic tongues. *A*, the tongue of patient S. L. (table 3); some fungiform papillary structure remains. Compare with *B*, the tongue of patient M. L. (table 3). *C*, same tongue as *A* after the patient had one month's treatment with iron sulfate, nicotinic acid and riboflavin. There is considerable growth of filiform papillae and hypertrophy of the fungiform papillae. *D*, same tongue as *B* after the patient had three months' treatment with large doses of nicotinic acid and riboflavin. There is no change in surface structure; hence the tongue of *A* must have been desquamated, the tongue of *B* atrophied.

SUMMARY AND CONCLUSIONS

A method has been described which permits accurate printing of the distal third of the tongue. This has been made possible by development of an ink which is nonpoisonous, tasteless, of the proper con-

sistency and fast drying. Prints obtained withstand scrutiny with low powers of the microscope and render clear and permanent the detail of the filiform and fungiform papillary structure of the tongue. The underlying folds and creases in the mucous membrane of the tongue are also defined in the prints.

The tongue prints of a group of 99 normal, healthy male medical students were studied by this method. Counts of the filiform and fungiform papillae were made and averaged 52.2 for the former and 8.1 for the latter. It was found that these tongues could be grouped into five distinct types. In the order of frequent occurrence, these types were filiform, fungiform, slightly fissured, fissured and linear.

Prints of the tongues of a group of 15 patients with definite dietary deficiencies and those of a group of 7 patients with pernicious anemia were compared with those of the normal group. It was found that there was a pronounced decrease in the count of filiform papillae and a slight increase in the number of fungiform papillae. Two other distinctly abnormal features, a crosshatched pattern and longitudinal ridging, never found in the normal group, are described and their significance discussed. The tongues of the group of patients with dietary deficiencies could not be distinguished from those of the group of patients with pernicious anemia.

A plea is made for a classification of the abnormal tongue based on the fundamental structure of the lingual surface, i. e., the papillae. This classification recognizes only three groups: the normal tongues, which have intact papillae as to both number and structure; the desquamated tongues, which have a pronounced decrease in filiform papillae but have their fungiform papillae intact, and the atrophic tongues, in which there is complete absence of filiform papillae and a decided decrease in fungiform papillae.

RETINAL AND CHOROÏDAL ARTERIOLES IN MALIGNANT HYPERTENSION

A Clinical and Pathologic Study of Fifteen Cases *

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SINCE Richard Bright,¹ in 1836, described the renal syndrome which came to bear his name, innumerable authors have contributed to the clarification and classification of renal disease and hypertension. Johnson,² in 1868, was the first to describe the presence, in cases of Bright's disease, of a diffuse disease of the smallest arteries characterized by hypertrophy of the media.

At the Mayo clinic, since the papers of Keith³ and Keith, Wagener and Kernohan,⁴ a number of studies⁵ have served to emphasize the diffuse nature of hypertensive vascular disease. Beginning with the work of Kernohan, Anderson and Keith,⁶ an attempt has been made to establish the normal thickness of the wall of an arteriole as compared

* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine.

1. Bright: Cases and Observations, Illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine, *Guy's Hosp. Rep.* **1**:338-400, 1836.

2. Johnson, G.: On Certain Points in the Anatomy and Pathology of Bright's Disease of the Kidney: II. On the Influence of the Minute Blood-Vessels upon the Circulation, *Med.-Chir. Tr.* London **51**:57-78, 1868.

3. Keith, N. M.: Classification of Hypertension and Clinical Differentiation of the Malignant Type, *Am. Heart J.* **2**:597-608 (Aug.) 1927.

4. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, *Arch. Int. Med.* **41**:141-188 (Feb.) 1928.

5. (a) Cain, E. F.: Malignant Hypertension: The Histologic Changes in the Kidneys, *Arch. Int. Med.* **53**:832-850 (June) 1934. (b) Kyser, F. A.: Relationship of Essential Hypertension to Pathologic Changes in the Thyroid Gland, Thesis, Graduate School of the University of Minnesota, 1940. (c) Morlock, C. G.: Arterioles of the Pancreas, Liver, Gastro-Intestinal Tract and Spleen in Hypertension, *Arch. Int. Med.* **63**:100-118 (Jan.) 1939. (d) Odel, H. M.: Structural Changes in Arterioles of Myocardium in Diffuse Arteriolar Disease with Hypertension Group 4, *ibid.* **66**:579-602 (Sept.) 1940. (e) Rosenberg, E. F.: The Brain in Malignant Hypertension: A Clinicopathologic Study, *ibid.* **65**:545-586 (March) 1940.

6. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, *Arch. Int. Med.* **44**:395-423 (Sept.) 1929.

with its lumen and to determine what changes are to be found in hypertension. With a few notable exceptions, to be discussed later, it has been found that although the wall-lumen ratio varies radically in different organs hypertension is uniformly accompanied with a definite reduction of the ratio of the diameter of the lumen to the thickness of the wall. The degree to which it is reduced increases as the severity of the hypertension increases. Furthermore, this reduction has appeared in many instances to be of sufficient degree to present a definite impediment to the flow of blood.

Although, as noted, numerous papers have been concerned with the pathologic anatomy of hypertensive disease, only a few detailed studies of the eyes have been reported.

TABLE 1.—*Summary of Clinical and Pathologic Data on Controls*

Age, Yr.	Sex	Pathologic Diagnosis	Highest Recorded Blood Pressure, Mm. Hg		Body Weight, Lb.	Heart Weight, Gm.	Normal Heart Weight, Gm.*	
			Systolic	Diastolic			Maximum	Minimum
41	M	Lymphoblastoma	130	90	185	350	382	296
57	F	Hyperthyroidism	Preop. 132 Crisis 165	80 112	135	275	286	203
23	F	Torula meningitis	140	80	180	320	356	301
50	F	Ruptured cerebral aneurysm	134	106	150	310	313	225
20	F	Polyneuritis	150	90	121	260	259	215
55	F	Carcinoma of breast	130	80	140	280	295	253
43	F	Carcinoma of com- mon bile duct	100	50	165	237	337	247

* Normal heart weight means the weight of the heart of a normal person of the same age, sex and body weight as the subject (Sec Smith, H. L.: Relation of Weight of Heart to Weight of Body and of Weight of Heart to Age, *Am. Heart J.* 4: 79-93 [Oct.], 1928).

The present study is concerned with eyes which were obtained at necropsy in 15 cases of malignant hypertension. The work was directed mainly toward lesions of the arterioles and more particularly to a determination of the change which might be found in the wall-lumen ratio of arterioles of the retina and the choroid. Seven additional cases were selected as controls, in which neither the history nor the physical examination showed any evidence of hypertension (table 1).

REVIEW OF LITERATURE

Bright,¹ in his paper of 1836, remarked that patients who have nephritis often suffer from visual impairment.

Türck,⁷ in 1850, first reported microscopic lesions in the eyes of nephritic patients when he found "an exudative process" with the presence of "granular cells in the posterior portion of the retina."

7. Cited by Greear.²⁰

Liebreich⁷ described "albuminuric retinitis," and Weeks⁸ found that in such cases there was irregular hyaline degeneration of the retinal and choroidal arteries with encroachment on the lumen.

In cases of angiosclerosis, Coats⁹ found eccentric proliferation of the endothelium with narrowing of the lumen.

Leber¹⁰ stated that in cases of retinitis due to nephritis the central retinal and posterior ciliary arteries showed medial hypertrophy.

Cohen,¹¹ in reporting the histologic changes in the eyes in 18 cases of "general arterial and kidney diseases," included 3 cases of malignant hypertension. In these he found severe sclerosis of the choroidal arterioles, compared with moderate sclerosis of the retinal arterioles. The vascular changes were not proportionate to those seen ophthalmoscopically.

Wagener,¹² in 1927, described the retinopathy of malignant hypertension and included histologic studies of 3 cases. The retinal arterioles were thickened principally by perivascular fibrosis. There was slight medial hypertrophy but no intimal hyperplasia. The internal elastic lamina was slightly thickened. Choroidal arteriosclerosis was more severe than retinal, and there were also medial hypertrophy and endothelial hyperplasia. In some cases the lumen was occluded by retinal proliferation, while in others it was filled with fatty granular cells.

Verwey¹³ gave a detailed report of the histologic changes in 1 case of albuminuric retinitis. His observations were essentially the same as Wagener's. Fat staining showed the arteriolar walls thickened by deposits of lipid material.

Keith, Wagener and Kernohan,⁴ in a study of malignant hypertension, found the choroidal to exceed the retinal arteriosclerosis. The retinal arterioles were thickened mainly by medial hypertrophy and perivascular fibrosis, while in the choroidal arterioles the main change was

8. Weeks, J. E.: A Contribution to the Pathology of Albuminuric Retinitis, *Arch. Ophth.* **17**:276-294, 1888.

9. Coats, G.: Intraocular Vascular Disease, *Ophthalmoscope* **4**:605-621 (Nov.) 1906.

10. Leber, T.: Die Krankheiten der Netzhaut, in Graefe, A., and Saemisch, T.: *Handbuch der gesamten Augenheilkunde*, Leipzig, Wilhelm Engelmann, 1915, vol. 7A, pt. 1, pp. 101-106.

11. Cohen, M.: Significance of Pathologic Changes in Fundus in General Arterial and Kidney Diseases, *J. A. M. A.* **78**:1694-1698 (June 3) 1922; Choroid-retinal Arteriolar Necrosis in Malignant Hypertension: Report of a Case, *Arch. Ophth.* **23**:1052-1059 (May) 1940.

12. Wagener, H. P.: The Retinitis of Malignant Hypertension, *Tr. Am. Ophth. Soc.* **25**:349-380, 1927.

13. de la Fontaine Verwey, B. C.: Ueber die Arteriosklerose der Netzhaut und ihre Bedeutung für die Genese der Retinitis albuminurica, *Klin. Monatsbl. f. Augenh.* **79**:148-158 (Sept. 2) 1927.

intimal proliferation, with less striking medial hypertrophy and perivascular fibrosis.

Friedenwald¹⁴ stated that the vascular lesions of albuminuric retinitis are the same as those of malignant hypertension. He emphasized the occurrence of acute necrosis with hyalinization and the diffusion of lipoid material in the arteriolar walls.

In cases of albuminuric retinitis Kyrieleis¹⁵ found arteriosclerotic changes present consistently in the optic disk but not in the retina.

Moritz and Oldt¹⁶ found that in the eye arterioles having an external diameter of 50 to 100 microns showed intimal hyalinization. In those vessels larger than 50 microns there was frequently also endothelial proliferation.

Gasteiger¹⁷ in cases of malignant nephrosclerosis found the retinal arterioles thickened by fat infiltration, accompanied with a decrease of the lumen. Similar but more severe changes were seen in the choroidal arterioles.

Koyanagi,¹⁸ some of whose cases appear to have been cases of malignant hypertension, found that the arterioles of the optic disk and the surrounding retina showed severe endothelial proliferation and hyalinization leading to obliteration of the lumen. There were similar severe changes in the choroidal arterioles.

Magitot and Dubois-Poulsen,¹⁹ in a case of malignant hypertension, found patchy arteriolar lesions which were more severe in the choroid than in the retina. There were intimal proliferation with encroachment on the lumen, fat infiltration of the proliferated cells and medial hypertrophy.

Greear²⁰ found medial hypertrophy and hyalinization in the retinal arterioles and more severe changes in the choroidal arterioles.

14. Friedenwald, H.: Pathological Changes in the Retinal Blood-Vessels in Arterio-Sclerosis and Hypertension, *Tr. Ophth. Soc. U. Kingdom* **50**:452-531, 1930.

15. Kyrieleis, W.: Ueber die Arteriolosklerose von Netzhaut, Aderhaut und Sehnerv sowie ihre Bedeutung für die Pathogenese der Retinitis albuminurica, *Arch. f. Augenh.* **103**:161-198 (June) 1930.

16. Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Nonhypertensive Individuals, *Am. J. Path.* **13**:679-728 (Sept.) 1937.

17. Gasteiger, H.: Ueber histologische Befunde am Auge bei Nieren- und Blutdruckveränderungen, *Klin. Monatsbl. f. Augenh.* **99**:604-625 (Nov.) 1937.

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Agatston²¹ found arterioles of the eyes of hypertensive persons to show hyaline degeneration of the intima, swelling of the subendothelial collagen and thickening of the media due to increase of muscle or increase of collagen or both.

CLINICAL STUDIES

Fifteen cases of malignant hypertension were studied. The patients were 1 white woman, 1 Negro man and 13 white men. Their ages varied from 22 to 65 as shown in table 2.

The duration of the disease from the onset of symptoms to death ranged from five weeks to sixty-nine months, with the average duration of sixteen months. One patient (case 13) had been known to have hypertension for two years but had had symptoms only during the last six months of his illness.

The past medical history contributed information in only 4 cases (4, 6, 8 and 9). Besides the usual childhood exanthems, typhoid and

TABLE 2.—*Age Distribution of Patients Who Had Malignant Hypertension*

Age, Yr.	Patients
20-29.....	2
30-39.....	3
40-49.....	1
50-59.....	7
60-69.....	2

pneumonia each occurred twice; rheumatic fever and pleurisy with effusion occurred once. In no case was there an antecedent history of glomerulonephritis.

The family history revealed hypertension in one or both parents in cases 3, 6 and 10 and in two siblings in case 11.

The first symptoms to appear were renal in 6 cases (frequency, nocturia or hematuria) and cardiac in 5 cases (dyspnea). Headache, confusion and loss of visual acuity account for the remainder. In table 3 the most significant symptoms are listed in the order of their frequency of occurrence. In 1 case (case 11), in which the onset of symptoms resembled renal colic, the patient had been found at operation to have an aneurysm of the renal artery, and nephrectomy had been done. In another (case 15), in which the first symptom was painless hematuria, ureterolithiasis of the left side and atrophic kidney were observed at necropsy.

A physical examination revealed in each case a noticeable elevation of the blood pressure, with the maximal systolic pressure varying from

21. Agatston, S. A.: Relation of Vascular Disease to Retinitis, *M. Rec.* **153**: 303-306 (May 7) 1941.

220 to 350 mm. of mercury and the maximal diastolic pressure from 140 to 200 mm.

In every case there was retinopathy of malignant hypertension.

Cardiac enlargement was found in every case and sclerosis of the peripheral arteries (radial, brachial or temporal) in all but 3 cases (5, 8 and 15). Disturbances of cardiac rhythm were recorded in 9 cases: tachycardia in 6, gallop rhythm in 3, extrasystoles in 2 and auricular fibrillation in 1. The aortic second sound was accentuated in 9, and an aortic systolic murmur was heard in 6. A pericardial friction rub was heard in 2 cases (2 and 6). Manifestations of cardiac failure occurred in 10 cases. Pulmonary congestion was present 9 times, enlargement of the liver 5 times, edema and cyanosis each 4 times and ascites once.

Signs referable to the central nervous system were present in 10 instances. Cheyne-Stokes respirations were observed eight times, con-

TABLE 3.—*Symptoms in Cases of Malignant Hypertension*

Symptoms	Frequency *
Cardiac.....	22
Dyspnea, edema, ascites, palpitations	
Central nervous system.....	18
Headache, confusion, coma, stupor, convulsions, paralysis	
General.....	15
Generalized weakness, loss of weight	
Visual.....	10
Blurring, partial to complete blindness	
Renal.....	9
Urinary frequency, nocturia, hematuria	
Gastrointestinal.....	3
Nausea and vomiting, diarrhea, gastrointestinal bleeding	

* Frequency means the total frequency of symptoms of this group.

vulsions twice, hemiplegia twice and muscular twitchings once. Enlargement of the thyroid gland was recorded in 2 cases.

LABORATORY STUDIES

The maximal specific gravity of the urine varied from 1.006 to 1.025 and the minimum from 1.004 to 1.015. In only 3 cases was the specific gravity as great as 1.020. Albuminuria was absent in only 1 case; in 4 it was graded 1 or 2 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition) and in the remaining 10 it was 3 to 4. In 4 cases there were no erythrocytes in the urine, while in the remainder the grade varied from 1 to 4. Casts were present in the urine in only 5 cases, and then there were only a few of the granular or the hyaline type.

The concentration of hemoglobin varied from 8.5 to 14.7 Gm. per hundred cubic centimeters of blood in the 14 cases in which it was determined. Leukocytes varied from 5,800 to 19,200 per cubic millimeter of

blood, and there was more than a maximal normal of 10,000 in 7 of the 14 cases in which they were determined. Erythrocytes varied from 2,250,000 to 4,770,000 per cubic millimeter of blood. In 7 cases there was definite anemia as indicated by either a concentration of hemoglobin of less than 12.0 Gm. per hundred cubic centimeters of blood or an erythrocyte count of less than 4,000,000 per cubic millimeter of blood. The concentration of urea was less than 40 mg. per hundred cubic centimeters of blood on admission in only 2 cases (1 and 11), and in each of these it became elevated terminally. The concentration of urea ranged from 33 to 304 mg. per hundred cubic centimeters of blood on admission and from 84 to 492 mg. per hundred cubic centimeters terminally. Terminal concentrations of creatinine varied from 3.0 to 19.2 mg. per hundred cubic centimeters of blood in the 13 cases in which they were determined. Serum sulfates were determined in 6 cases and varied from 5.0 to 49.0 mg. per hundred cubic centimeters of serum. They were definitely more than 5.5 mg. in 5 of the 6 cases in which they were determined.

The concentration of chlorides, determined in 8 cases, was normal in all except 1 (case 14), in which it was subnormal (464 mg. per hundred cubic centimeters of plasma).

The carbon dioxide-combining power was sufficiently depressed to indicate definite acidosis (less than 40 volumes per hundred cubic centimeters of plasma) in only 2 of the 11 cases in which it was determined, but it was less than 50 volumes per hundred cubic centimeters of plasma in an additional 4 cases.

The concentration of potassium was determined in 3 cases and was elevated in 2 (normal 17 to 21 mg. per hundred cubic centimeters of serum).

The serologic reaction of the blood for syphilis was negative in the 12 cases in which it was determined.

Electrocardiograms were taken in 11 cases, and each showed some deviation from the normal. Preponderance of the left ventricle was seen in 6 cases. Changes of the T wave (diphasic or inverted) were found in 8 cases. They were present in lead I alone in 3 cases; they were present in all three standard leads in 4 cases, and in 1 case they were present in leads I, II and IV. Slurring of the QRS complex was present twice in all three standard leads and twice in leads I and III alone. The S-T segment was elevated in CR2 once and depressed once. The clinical and laboratory data are summarized in table 4.

SUMMARY OF GROSS PATHOLOGIC STUDIES

The known duration of the disease from the onset of symptoms to death varied from five weeks to sixty-nine months, with an average duration of sixteen months. The primary cause of death was cardiac failure

TABLE 4.—Summary of Clinical and Laboratory Data: Malignant Hypertension

Case	Yr.	Age.	Sex	Date of Admis- sion	Blood Pressure, Mm. of Mercury				Specific Gravity			Urine			Blood											
					Maximum		Minimum		S.	D.	S.	D.	Albumin, Grade *	Erythrocytes, Grade *	Casts, Grade *	Hemoglobin, Gm. per 100 Cc.	Erythrocytes per Cu. Mm.	Leukocytes per Cu. Mm.	Urea, Mgr. per 100 Cc.	Creatinine, Mgr. per 100 Cc.	Sulfates, Mgr. per 100 Cc. of Serum	Chlorides, Mgr. per 100 Cc. of Plasma	Potassium, Mgr. per 100 Cc. Serum	Plasma CO ₂ - Combining Power, Vol per 100 Cc.	Flocculation Test for Syphilis	
					S.	D.	S.	D.																		Maxi- mum
1	55	F		12/ 0/23	260	160	210	130		1.018	1.009	1-3	0	0-1	13.2	4.71	10,400	33	1.8	Neg.	
2	50	M		11/13/24	220	140	184	90		1.013	1.013	0	0	0	8.6	2.43	19,200	201 to 255	7.4 to 19.1	Neg.	
3	65	M		8/11/25	280	150	188	108		1.018	1.012	1	0	0	11.5	3.05	16,800	40 to 101	4.5 to 4.5	45 to 53		
4	50	M		1/27/27	260	180	180	90		1.000	1.006	1-2	0-1	0	14.7	3.17 to 4.00	16,800	88 to 188	4.3 to 6.5	...	650	...	55	Neg.		
5	22	M		5/ 5/33	350	190	244	162		1.000	1.008	3	3	0	12.3	4.06	8,400	66 to 108	3.8 to 9.0	...	479	..	46.6	Neg.		
6	20	M		10/ 4/33	240	150	164	75		1.021	1.010	3	2-4	1-1+† 1-3†	8.5	2.34	6,400	144 to 492	9.0 to 17.2	15.0 to 17.0	520	..	62.0	Neg.		
7	55	M		8/21/34	290	190	104	110		1.014	1.010	3	1	0	10.4	3.71	8,700	154 to 285	6.4 to 8.4	17.7	39.0	Neg.		
8	32	M		2/11/35	240	140	190	86		1.011	1.007	3-4	2-4	0	9.8	3.03	11,200	152 to 324	10.8 to 18.8		
9	32	M		11/14/38	220	140	190	110		1.012	1.010	3	0-2	0	2.25	5,800	304 to 314	16 to 19.2	35.7 to 49.0	544 to 606	23.7	40.0		
10	33	M		1/ 2/40	250	162	210	108		1.015	1.008	2-4	1	0	8.5	6,600	160 to 284	6.8 to 10.4	538	..	59.8	Neg.		
11	51	M		2/ 4/42	200	160	180	118		1.025	1.011	2	1	0	12.1	6,500	34 to 84	Neg.		
12	63	M		4/21/43	260	170	180	125		1.020	1.015	2-4	0-1	0-1	14.0	8,300	42 to 170	1.8 to 3.0	5.0	594	..	58.9	Neg.		
13	53	M		9/ 1/43	260	160	230	130		1.012	1.006	2	0	0	12.5	213 to 318	8.0 to 6.3	23.2	611	18.7	44.7	Neg.		
14	53	M		11/ 1/44	245	200	200	120		1.014	1.004	4-1	1-2	0-2	12.5	4.08	10,300	128 to 324	6.3 to 11.6	14.0	464	33.4	31.0	Neg.		
15	43	M		12/10/43	230	150	85	65		1.015	3	4	1	12.3	4.77	11,600	72 to 130	41.0	Neg.		

* The grade was on a basis of 1 to 4.

† This cast was hyaline.

‡ These casts were granular.

in 4 cases, renal failure in 3, combined cardiorenal failure in 5 and cerebral hemorrhage in 2 cases. In the remaining case, a clinical diagnosis of cerebral hemorrhage was made, but this was not substantiated at necropsy. In addition, in 4 cases there were multiple small (up to 1.0 cm.) or petechial hemorrhages scattered widely through the brain, and in case 13 old infarcts were found in the basal ganglions.

Cardiac hypertrophy was found in every case, as may be seen by referring to the heart weights. In the cases of hypertension the weights ranged from 405 to 870 Gm. compared with a normal range of 275 to 393 Gm. In no case were valvular lesions found which could account for the hypertrophy. Patchy myocardial fibrosis was noted in 5 cases. In case 10 there was an acute infarction of the posterior papillaris muscle of the left ventricle. Coronary arteriosclerosis was found to be mild in 6 cases, moderate in 7 and severe in 2 cases. There was fibrinous pericarditis in 4 cases. Aortic arteriosclerosis was graded as mild in 3 cases, moderate in 8 and severe in 3; in 1 case the grade was not recorded. Pleural effusion was present in 5 instances and pericardial effusion in 2. Pulmonary edema was found 6 times.

The combined weights of the kidneys varied from 144 to 353 Gm. In case 4 a solitary left kidney weighed 166 Gm., while in case 11 the solitary right kidney weighed 185 Gm. In all cases except 2 (5 and 11), there were pitting and scarring of the surfaces of the kidneys. These data are summarized in table 5.

HISTOLOGIC STUDIES

In 3 cases of hypertension the eyes were prepared for sectioning by the celloidin²² method; in the remaining cases and in the controls the eyes were embedded in paraffin, and the usual fixation by means of solution of formaldehyde was used. Sections were cut so as to include the nerve head and the macular area. The tissues were stained with hematoxylin and eosin, Van Gieson's stain and elastin H stain.

In the control series, all the arterioles of both the retina and the choroid appeared normal (fig. 1). No lesions were seen which could be attributed to aging.

Cases of Malignant Hypertension.—(a) Vascular Lesions: 1. Intimal proliferation (subendothelial) occurred frequently and extensively in the arterioles of the choroid (fig. 2 A) but only rarely in those of the retina. It was seen in all but 3 of the cases and frequently resulted in partial or even complete obliteration of the lumen. Hyaline degeneration and fatty infiltration of the proliferated intima were seen occasionally.

22. Celloidin is a concentrated preparation of pyroxylin.

TABLE 5.—Summary of Pathologic Data on Malignant Hypertension

Duration of Life After Onset of Case Symptoms	Clinical Impressions as to Cause of Death	Heart Weight, Gm.	Normal Heart Weight, Gm.	Coro- nary Scler- osis *	Pericar- dialitis	Infarct	Myo- cardial Fibrosis	Aortic Scler- osis *	Cerebral Hemor- rhages	Pleural Effu- sion	Peri- cardial Effu- sion	Aseites	Pulmo- nary Edema	Com- bined Kidney Weight, Gm.	Pitted and Searred
1 5 yr. 9 mo.	Cardiac and renal failure	838	393	3	0	0	+	Severe	Multiple small	0	50 cc.	0	Right	300	+
2 3 mo.	Renal failure	623	284	2	+	0	0	1+	0	0	0	0	0	254	+
3 7 mo.	Cardiac failure	496	...	3	0	0	0	2+	Multiple small	0	0	0	0	206	+
4 1 yr.	Cardiac and renal failure	870	300	1	0	0	Slight	2	0	1,000 cc. left	150 cc.	0	0	Left only 163	+
5 7 mo.	Cerebral hemorrhage	722	300	1	0	0	0	1	Massive	0	0	0	+	270	0
6 9 mo.	Renal and cardiac failure	405	275	1	+	0	0	1+	Diffuse petechial	1,000 cc.	0	0	+	144	+
7 5 yr.	Cardiac failure	778	300	1	0	0	0	?	0	0	0	0	0	276	+
8 5 mo.	Renal failure	490	300	1+	0	0	0	1	Multiple petechial	+	0	0	+	...	+
9 2 mo.	Renal failure	595	300	1	0	0	0	1	0	250 cc. right	0	0	+
10 9 mo.	Cardiac and renal failure	640	300	2	+	+	0	1+	0	0	0	0	0	353	+
11 1½ yr.	Cerebral vascular accident	490	394	2	0	0	0	2	Massive	0	0	0	0	Right, only 185, com- pensatory hypert.	0
12 2 yr.	Cardiac failure	530	325	2	0	0	1	1+	0	0	0	0	0	243	+
13 6 mo.	Cardiac and renal failure	562	300	1	+	0	+	3	Old infarcts of basal ganglions	+	0	+	+	282	+
14 6 mo.	Cardiac failure	517	360	2	0	0	+	2	0	0	0	0	0	272	+
15 5 wk.	Cerebral hemorrhage not found at necropsy	595	323	2	0	0	0	2	0	0	0	0	0	308	+

* The sclerosis graded as 1 was mild; 1+ or 2, moderate, and 2+ or 3, severe.

2. Medial thickening due to hypertrophy of the muscle cells was seen in every case (fig. 2 *B* and 3 *A*). It was a considerable factor in decreasing the lumen in the retinal but not in the choroidal arterioles.

3. Around both the retinal and the choroidal arterioles an increase of the perivascular fibrous tissue, indistinguishable from the adventitia, was seen in a few instances.

4. Hyaline degeneration (fig. 3 *B*) of varying degree was seen frequently in the choroidal arterioles. This varied from small subendothelial deposits to involvement of the entire wall.

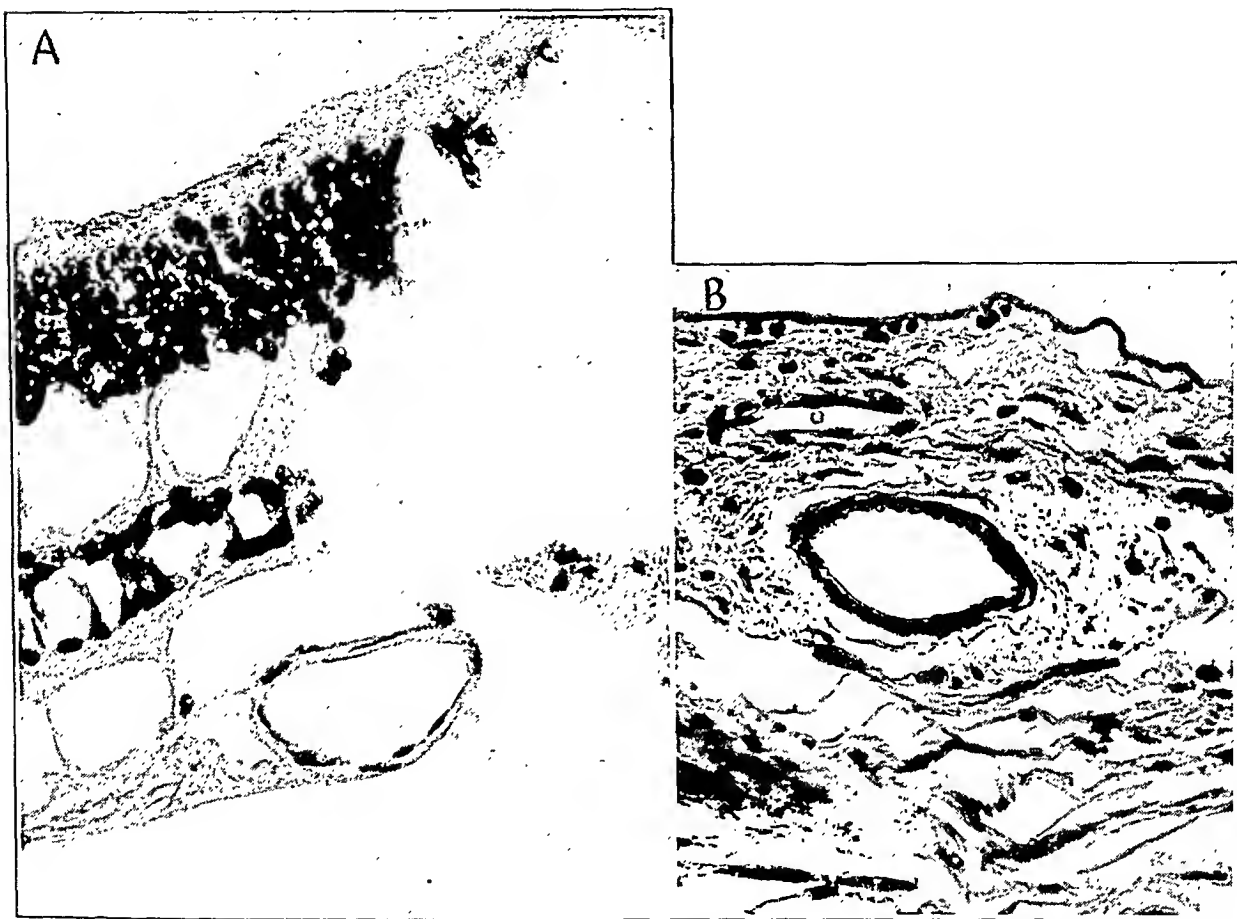


Fig. 1.—*A*, section of normal retinal arteriole (hematoxylin and eosin; $\times 365$).
B, section of a normal choroidal arteriole (hematoxylin and eosin; $\times 365$).

5. In a few choroidal arterioles there were smudgy granular areas which stained purple with hematoxylin and eosin, indicating acute necrosis. This most often occurred in the thickened intima, but in some instances it also involved the media.

An occasional choroidal arteriole showed infiltration (fig. 3 *C*) of its wall with fat, and some showed reduplication of the elastic lamina (fig. 3 *D*).

(b) Retinal Lesions: The histologic lesions, with the exception of those occurring in the arterioles, were found largely confined to an area around the nerve head, comprising about a sixth of the retina. Edema

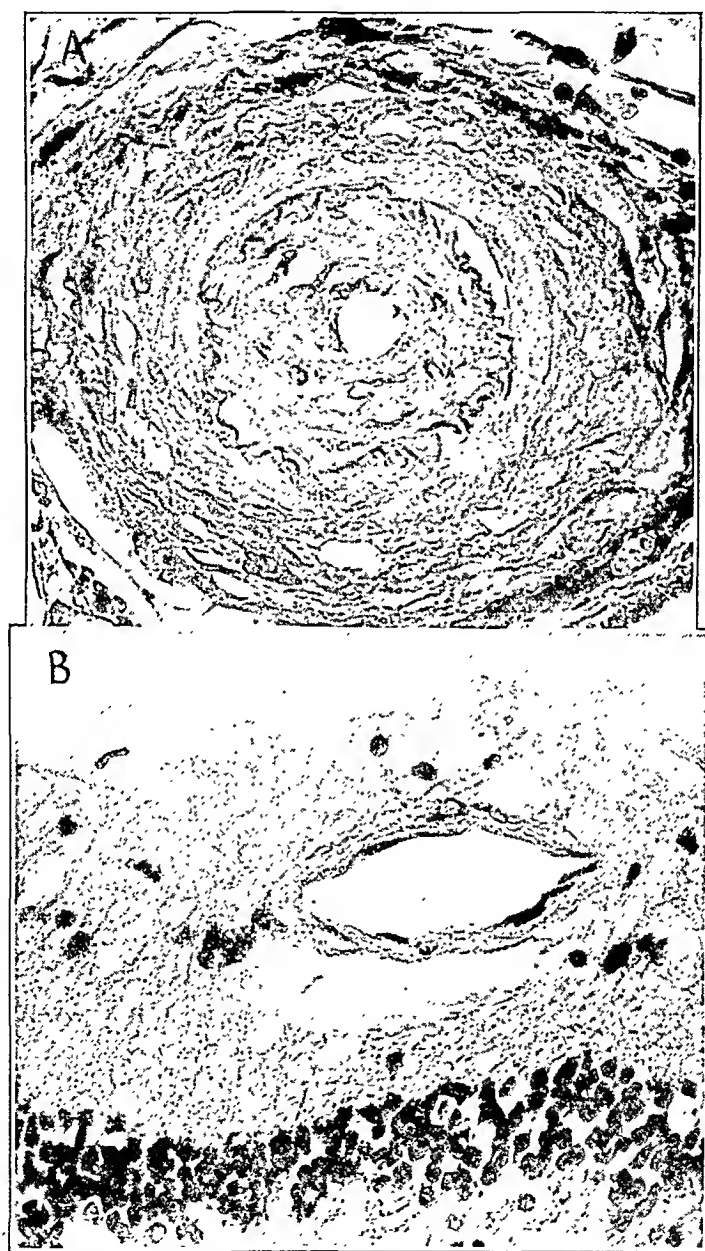


Fig. 2.—*A*, section of a choroidal arteriole of a patient with malignant hypertension (case 10), showing intimal proliferation, medial hypertrophy and perivascular fibrosis (Van Gieson's stain; $\times 365$). *B*, section of a retinal arteriole of the same patient, showing slight medial hypertrophy (hematoxylin and eosin; $\times 365$).

of the nerve head and of the peripapillary portion of the retina was seen in every case. The latter was the most striking of all the lesions seen.

In many cases it was of tremendous degree, producing great distortion of the retina, so that sometimes the retina was thrown into folds, with or without a collection of underlying fluid. In almost all cases there were varying numbers of cytoid bodies in the nerve fiber layers, as well as

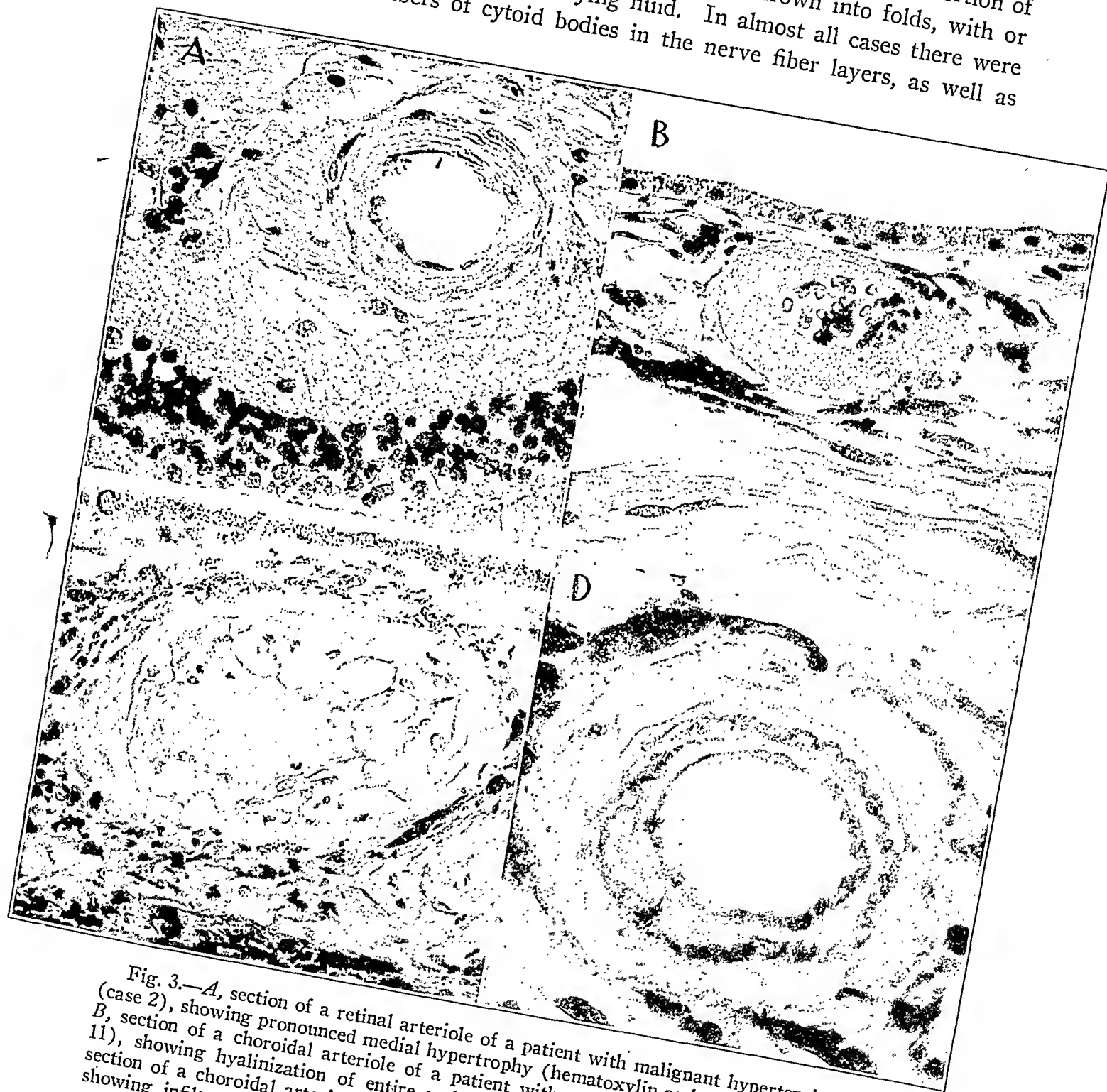


Fig. 3.—*A*, section of a retinal arteriole of a patient with malignant hypertension (case 2), showing pronounced medial hypertrophy (hematoxylin and eosin; $\times 365$). *B*, section of a choroidal arteriole of a patient with malignant hypertension (case 11), showing hyalinization of entire wall (hematoxylin and eosin; $\times 365$). *C*, section of a choroidal arteriole of a patient with malignant hypertension (case 1), showing infiltration of the wall with fat (hematoxylin and eosin; $\times 275$). *D*, section of a choroidal arteriole of a patient with malignant hypertension (case 7), showing thickening and fragmentation of the elastic lamina (elastin H; $\times 760$).

hemorrhages. The latter tended to spread along the fibers; hemorrhages that occurred in the deep layers were usually punctate and localized. Only a few hemorrhages were large enough to involve the whole thickness of the retina.

Albuminous exudates were almost entirely confined to the outer reticular layer, only occasionally spreading into the nuclear layers. They were sometimes surrounded by a rim of scavenger cells. A few of the latter were seen in the nuclear layers, but usually they were in the outer reticular layer, either singly or in clumps, which were of the same size and shape as the albuminous exudates.

Areas of fusiform degeneration of the nerve fiber layer were present in more than half the cases.

Subretinal edema, of the type described by Koyanagi¹⁸ as typical of cases of chronic nephritis, was seen in 7 cases. This consisted of a

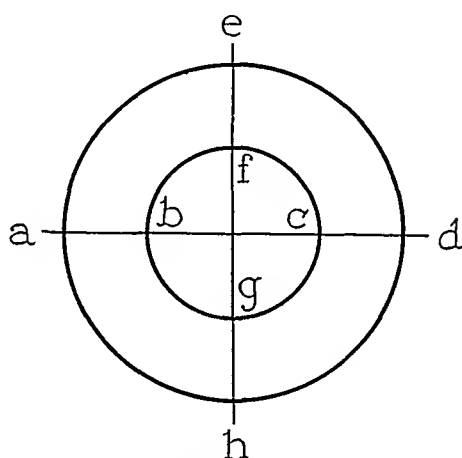


Fig. 4.—A cross section of a small artery or an arteriole, showing measurements on which the wall-lumen ratio is based.

collection of fluid adjacent to the optic nerve, raising the layer of rods and cones from the pigment epithelium.

Proliferation of the pigment cell layer was seen in only 4 cases and occurred as small knots of cells usually located in the peripheral portion of the retina.

The layer of rods and cones was notable for the fact that it was almost invariably normal.

(c) Measurement of Wall-Lumen Ratio: The procedure used by Kernohan was followed. Arterioles of 25+ to 120 microns in diameter, which had been cut at right angles to their course, were measured with a Bausch and Lomb micrometer. The manner of obtaining the wall-lumen ratio is illustrated in figure 4. The average²³ thickness of the

23. By "average" is meant the arithmetic mean of the total number of observations in each group.

wall, determined by averaging *a-b*, *c-d*, *e-f* and *g-h*, was divided into the average diameter of the lumen obtained by averaging *b-c* and *f-g*. In an effort to establish accurate ratios in each case, as many arterioles as were suitable were measured. The number measured varied greatly from case to case (table 6). In 3 controls and in 1 case of malignant

TABLE 6.—*Number of Arterioles Measured*

	Per Case	Total
Control retinal arterioles.....	1 - 7	16
Control choroidal arterioles.....	6 - 37	139
Hypertensive retinal arterioles.....	2 - 41	167
Hypertensive choroidal arterioles.....	7 - 74	410

TABLE 7.—*Summary of Wall-Lumen Ratios in Control Cases*

Retina		Choroid	
Observations	Average Ratio	Observations	Average Ratio
7	6.2	6	6.5
2	4.5	18	8.4
0	...	9	7.0
0	...	25	6.6
0	...	27	6.7
1	4.8	17	7.1
6	7.0	37	8.1
16*	5.6†	139*	7.2†

* This number represents the total.

† This number represents the average for all cases.

TABLE 8.—*Summary of Wall-Lumen Ratios in Cases of Malignant Hypertension*

Case	Retina		Choroid		Age of Patient, Yr.	Duration from Onset of Symptoms
	Observations	Average Ratio	Observations	Average Ratio		
1.....	23	2.8	17	1.24	55	5 yr. 9 mo.
2.....	8	2.4	7	0.9	50	3 mo.
3.....	41	1.8	18	1.6	65	7 mo.
4.....	4	1.2	13	1.5	50	1 yr.
5.....	4	2.6	29	2.4	22	7 mo.
6.....	22	3.2	74	3.3	29	9 mo.
7.....	0	...	10	1.2	55	5 yr.
8.....	16	3.1	68	3.2	32	5 mo.
9.....	2	5.0	12	4.5	32	2 mo.
10.....	4	2.2	60	2.6	33	9 mo.
11.....	15	3.0	24	5.4	51	1½ yr.
12.....	2	6.0	37	6.5	63	2 yr.
13.....	11	2.8	7	2.4	53	6 mo.
14.....	8	3.4	16	6.3	53	6 mo.
15.....	7	3.2	18	3.7	43	5 wk.
Total or average...	167	3.1	410	3.2		

hypertension no retinal arterioles were found which were suitable for measurement. When the number of retinal arterioles measured was small, this was due to the great frequency with which these exceedingly thin-walled vessels are distorted in sectioning.

These measurements show the average wall-lumen ratio of the retinal arterioles of the normal controls (table 7) to be 1:5.6, with variations

of 1:4.5 to 1:7.0. This is in distinct contrast to the cases of malignant hypertension (table 8), in which the average ratio was 1:3.1, with variations of 1:1.2 to 1:6.0 (figs. 5 and 6). Unfortunately, the number of normal retinal arterioles measured was too small to be considered

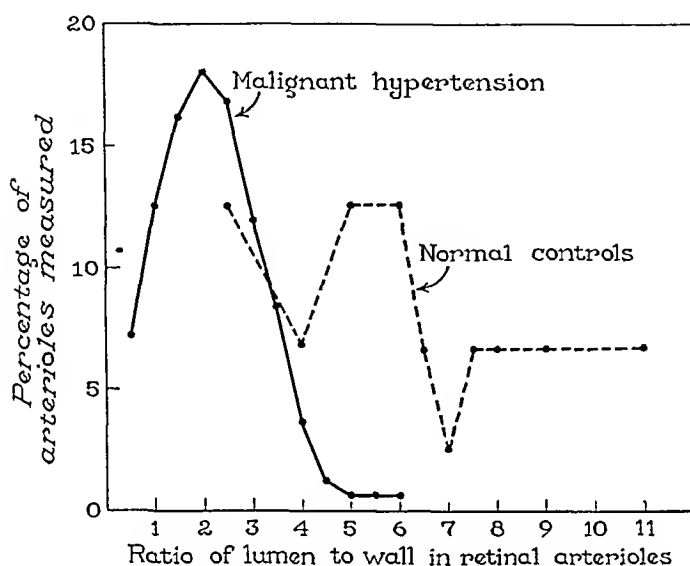


Fig. 5.—The frequency distribution of the ratio of wall to lumen in retinal arterioles.

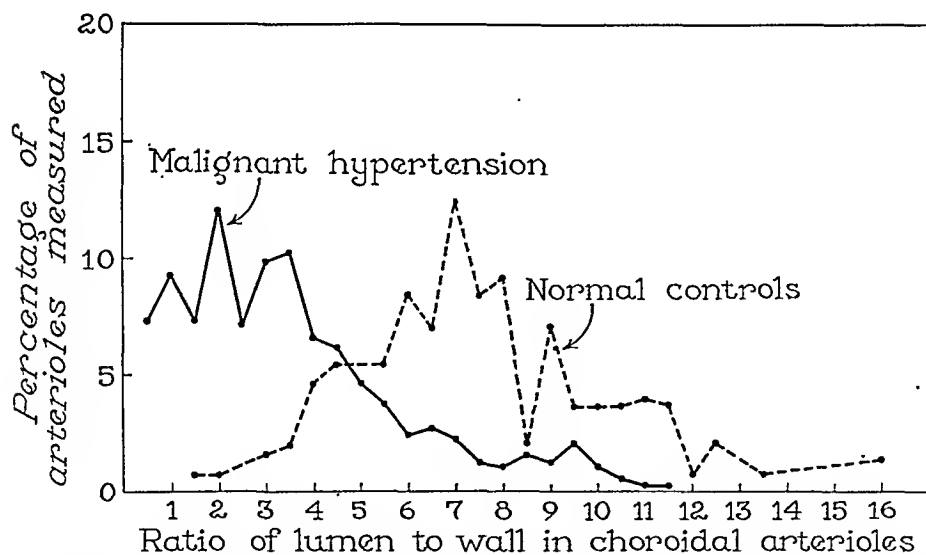


Fig. 6.—The frequency distribution of the ratio of wall to lumen in choroidal arterioles.

statistically significant. The choroidal arterioles produced similar findings. The average ratio for normal choroidal arterioles was found to be 1:7.2, with variations from 1:6.5 to 1:8.4. For the choroidal arterioles of patients who had malignant hypertension, on the other hand, the average ratio was 1:3.2, with variations of 1:0.9 to 1:6.5.

COMMENT

From the foregoing material it is evident that in the eyes, as in most other organs, malignant hypertension is accompanied with pronounced alteration of the structure of the arterioles. I was unable to demonstrate any relationship between the arterioles and the other retinal lesions. In fact, several cases in which there were great numbers of retinal hemorrhages and exudates were remarkable for the absence of any arteriolar disease except a little medial thickening. If the other retinal lesions in the eye in cases of this disease are the result of arteriolar disease, the causal relationship remains to be demonstrated.

It is noteworthy that intimal proliferation, seen so commonly in the choroidal arterioles, was seen only rarely in the retinal arterioles in my cases. This may have been due to the fact that the choroidal arterioles observed were, for the most part, of larger caliber than those seen in the

TABLE 9.—*Summary of Wall-Lumen Mean Ratios*

Organ	Wall-Lumen Ratio		Per Cent Reduction from Normal Mean of Wall-Lumen Ratio
	Control	Malignant Hypertension	
Spleen ^{5c}	1.32	1.04	21
Thyroid gland ^{5b}	1.68	1.30	23
Kidneys ^{5a}	1.80	0.7	61
Pectoral muscle ⁶	2.0	1.1	45
Heart ^{5d}	2.08	1.88	10
Gastrointestinal tract ^{5c}	2.13	1.14	46
Liver ^{5c}	2.31	1.14	50
Pancreas ^{5c}	2.45	1.24	49
Brain ^{5c}	3.5	1.70	51
Retina.....	5.6	3.1	45
Lungs ²⁴	3.5 - 7.0 (25 μ) (115 μ)*		
Choroid.....	7.2	3.2	56

* This is the outside diameter of the arteriole.

retina. However, since such changes were absent even in the largest retinal arterioles, this may not be the whole answer.

The last column of table 9 serves to emphasize the fact that the degree of arteriolar disease in malignant hypertension varies considerably in different organs. The greatest change occurred in the kidneys, in which the mean wall-lumen ratio was reduced by 61 per cent. Other organs which showed conspicuous change were: the choroid, 56 per cent; the brain, 51 per cent; the liver, 50 per cent, and the pancreas, 49 per cent. The heart, the spleen and the thyroid gland showed only slight changes of 10 to 23 per cent. These observations serve again to emphasize the diffuseness of the arteriolar disease in this type of hypertension.

SUMMARY AND CONCLUSIONS

The wall-lumen ratios of the retinal and choroidal arterioles measured in this series are greater than those of the arterioles measured in any

other organ studied by this method except the lung.²⁴ This is in accord with the work of Coats,⁹ who stated that the walls of arterioles observed in the eye are thinner than those in other organs.

The wall-lumen ratios of arterioles are definitely decreased in cases of malignant hypertension.

The most common manifestations of arteriolar lesions seen were medial hypertrophy and intimal proliferation. The choroidal vessels were much more affected than the retinal. Hyalinization of part or all of the arteriolar wall was seen frequently. Acute necrosis was seen occasionally.

No relationship was demonstrated between the arteriolar disease and other retinal lesions.

REPORT OF CASES

CASE 1.—A married white woman, 55 years of age, came to the Mayo clinic on Dec. 6, 1923, complaining of shortness of breath. She had been well until five years before admission, when recurrent bouts of shortness of breath, swelling of the ankles and nocturia began.

The past and the family histories contributed nothing of significance.

The systolic blood pressure was 210 mm. of mercury and the diastolic 160. A funduscopic examination revealed the retinopathy of malignant hypertension. The heart measured 3 by 13 cm., with a heaving precordial impulse and accentuation of the second aortic sound. There were rales at the bases of both lungs and pitting edema of the ankles. There was sclerosis of the peripheral arteries.

After two weeks of treatment in the hospital, the patient went home feeling well but returned on Sept. 14, 1924, complaining that for three months she had suffered from progressive dyspnea, weakness, edema, palpitations and periods of disorientation. Examination revealed the same conditions as before, plus anasarca. She failed rapidly and died on the fifth day after her admission to the hospital.

CASE 2.—A white man, 50 years of age, was admitted to the clinic on Nov. 13, 1924, complaining of shortness of breath and a cough. He had felt well until two and a half months before admission, when sudden attacks of dyspnea began, accompanied with a cough productive of frothy sputum. There had also been nervousness, blurred and dim vision and progressive loss of weight. During the week previous to admission there had been repeated attacks of vomiting, as well as swelling of the ankles.

The patient was cyanotic and orthopneic. The systolic blood pressure was 220 mm. of mercury and the diastolic 140. There were dulness on percussion and rales at the bases of both lungs, and the heart measured 4 by 14 cm. The abdomen was tensely distended, with the edge of the liver 6 cm. below the costal margin, and there was severe pitting edema of the legs and the back. The optic fundi showed the retinopathy of malignant hypertension.

The course was marked by progressive renal failure, uremic coma and death on the patient's fifteenth day in the hospital. A pericardial friction rub was heard on the day before the patient died.

CASE 3.—A white merchant, 65 years of age, was brought to the clinic on Aug. 11, 1925, because seven months before this time he had had a sudden

24. Kaump, D. H., and Dry, J. J.: Pulmonary Arteriolar Sclerosis: A Clinicopathologic Study, *Arch. Int. Med.* 61:1-18 (Jan.) 1938.

"general breakdown," marked by extreme weakness and loss of memory. His blood pressure at that time was stated to have been 250 to 280 mm. of mercury. Progressive mental deterioration, bouts of delirium, noticeable dyspnea and visual failure had developed. At times the patient had passed blood in his stools.

The patient was hyperactive, dyspneic and confused. The optic fundi presented the retinopathy of malignant hypertension. The heart measured 3.5 by 11.5 cm., and auricular fibrillation was present. Systolic and diastolic murmurs were heard in the mitral area, and a systolic murmur was heard in the aortic area. Rales were heard at the bases of both lungs.

The course was marked by progressive pulmonary congestion, coma and death on the patient's eighth day in the hospital.

CASE 4.—A white man, 50 years of age, was admitted to the hospital on Jan. 27, 1927, because of severe dyspnea. His illness had begun one year before with nocturnal attacks of "asthma," followed by increasing urinary frequency, nocturia, dyspnea on effort, swelling of the ankles and abdominal distention.

The patient was orthopneic and had severe edema of the legs and the back. The systolic blood pressure was 220 mm. of mercury and the diastolic 140. The optic fundi showed the retinopathy of malignant hypertension. Sclerosis of the peripheral arteries was graded 2. The heart measured 3 by 15 cm., and the pulmonic second sound was accentuated. Rales were heard at the bases of both lungs, and there was fluid in the abdomen.

The course was marked by gradually progressive cardiac and renal failure, with terminal convulsions, fibrillary muscular twitching, Cheyne-Stokes respirations, coma and death five weeks after the patient's admission to the hospital.

CASE 5.—A white farmer, 22 years of age, came to the clinic on May 5, 1933, complaining that six months previously urinary frequency and nocturia had developed, followed by swelling of the ankles, fatigue and dimness of vision.

The systolic blood pressure was 244 mm. of mercury and the diastolic 162. Funduscopy examination showed the retinopathy of malignant hypertension, and the heart was slightly enlarged.

The patient went home, but four weeks later he was brought back to the hospital with the story that one week previously scotomas, periods of loss of all except central vision and severe headaches had begun. On the day of admission he had suddenly collapsed and passed into coma.

Physical examination revealed a comatose patient with Cheyne-Stokes breathing. There were divergent strabismus and unequal pupils, and the extremities were spastic on the right side. The clinical diagnosis was cerebral hemorrhage. The patient died suddenly, three hours after his admission to the hospital.

CASE 6.—A white clerk, 29 years of age, came to the clinic on Oct. 4, 1933, because nine months previously blurred vision and a blood pressure of "200" had developed, followed by severe headaches in the morning, vomiting spells, progressive loss of weight, nocturia, fatigue and palpitations.

The systolic blood pressure was 240 mm. of mercury and the diastolic 150. The optic fundi showed the retinopathy of malignant hypertension. The heart measured 3 by 10 cm.; the aortic second sound was accentuated, and there was an aortic systolic murmur. Moist rales were heard at the bases of the lungs. Sclerosis of the peripheral arteries was graded 3.

The course was marked by small urinary output (120 to 650 cc. daily), stupor and coma, with death occurring on the twelfth day after the patient's admission to the hospital. A precordial friction rub appeared four days before the patient died.

CASE 7.—A white man, 55 years of age, came to the clinic on Aug. 21, 1934. He stated that he had been well until five years before, when, because of nocturia and dyspnea, he had consulted a physician, who found him to have hypertension. During the past year, because of fulness in the neck, tremor, increasing nervousness, loss of weight and an elevated basal metabolic rate, he had been thought to have goiter. There had been no response to treatment with iodine. Six months previously, the vision in his right eye had become suddenly clouded, after which he had progressive weakness, dyspnea, cough and substernal pain on effort.

The patient was orthopneic and hyperactive, and the breath bore a urinous odor. There was considerable tremor of the hands. Both lobes of the thyroid gland were enlarged and nodular. The heart measured 3 by 12 cm., and there was a gallop rhythm. The aortic second sound was greatly accentuated, and there was an aortic systolic murmur. There were rales at the bases of both lungs, and the liver extended 6 cm. below the costal margin. The optic fundi showed the retinopathy of malignant hypertension.

The patient exhibited progressive cardiorenal failure and passed into coma. Cheyne-Stokes breathing developed, and he died on the sixth day in the hospital.

CASE 8.—A white man, 32 years of age, who came to the clinic on Feb. 11, 1935, had been well until five months previously, when nocturia, gross hematuria and pain in both loins had begun, followed by severe headaches and episodes of vomiting. For two and a half months vision in both eyes had been much impaired. Three weeks previously, the patient had had a generalized convulsion lasting fifteen minutes, following which he had had a persistent internal squint and progressive weakness.

The patient was weak and sallow. The systolic blood pressure was 240 mm. of mercury and the diastolic 140. The right eyeball was turned inward, and the fundi showed the retinopathy of malignant hypertension. The heart was enlarged, and the aortic second sound was greatly accentuated.

The patient failed rapidly and died in uremic coma nine days after his admission to the hospital.

CASE 9.—A white farmer, 32 years of age, came to the clinic on Nov. 14, 1938. Morning headaches of a severe type and nocturia had begun two months previously, followed by progressive visual failure, nausea, vomiting, diarrhea, puffiness of his face and palpitations.

The systolic blood pressure was 220 mm. of mercury and the diastolic 130. Sclerosis of the peripheral arteries was graded 3. The heart measured 3.5 by 11 cm., and there was a heaving precordial murmur. Funduscopic examinations showed the retinopathy of malignant hypertension.

The patient failed progressively, became comatose and died on the eighth day in the hospital.

CASE 10.—A Negro, 33 years of age, came to the clinic on Jan. 2, 1940, complaining that nine months before this time severe fronto-occipital morning headaches had begun, followed by blurred vision, nausea and vomiting, easy fatigue, dyspnea on effort and progressive loss of weight. He had been known for six months to have hypertension and albuminuria.

The patient was thin and sickly looking, and his breath smelled of urine. The systolic blood pressure was 240 mm. of mercury and the diastolic 160. The left border of the heart measured 11 cm.; the aortic second sound was greatly accentuated, and gallop rhythm was present. Sclerosis of the peripheral arteries was graded 3. Funduscopic examination revealed the retinopathy of malignant hypertension.

The patient's course was marked by progressive cardiorenal failure, and he died on the twelfth day in the hospital.

CASE 11.—A white man, 51 years of age, came to the clinic on Feb. 4, 1942. He stated that he had been well until one and a half years before, when he had experienced a sudden attack of pain in the left flank extending to the groin, dysuria and urinary frequency. After two weeks of constant pain, nephrectomy had been done on the left side. He was told that he had had an aneurysm of the renal artery and that he had hypertension. He had been weak ever since this operation. In the five months before his admission to the clinic severe occipital headaches, nocturnal attacks of dyspnea, swelling of the ankles, vomiting and clouded sensory perception had developed. Two weeks previously he had had a sudden attack of unconsciousness lasting four hours, followed by persistent clouding of vision.

The systolic blood pressure was 220 mm. of mercury and the diastolic 120. The heart was enlarged, and the pulmonic second sound was greater than the aortic second sound. Sclerosis of the peripheral arteries was graded 3. The optic fundi showed the retinopathy of malignant hypertension.

The patient had repeated bouts of severe headache, accompanied with nausea and vomiting. Two weeks after his admission to the hospital, he suddenly passed into coma and had several convulsions. Right hemiplegia developed. He died fifteen days after admission.

CASE 12.—A white man, 63 years of age, came to the clinic on April 21, 1943. He stated that he had been well until two years before, when he noted a sudden diminution of visual acuity followed by gradually increasing weakness and impairment of memory. For six weeks, he had had severe headaches in the morning and for two weeks he had stumbled frequently in walking.

The systolic blood pressure was 260 mm. of mercury and the diastolic 158. The patient was mildly ataxic. The heart was enlarged, and the pulmonic second sound was greater than the aortic second sound. Sclerosis of the peripheral arteries was graded 2. Examination with the funduscope revealed the retinopathy of malignant hypertension.

Three days after hospitalization the patient became disoriented. This was followed by increasing tachycardia, Cheyne-Stokes breathing, rise of temperature to 102 F. and death on the tenth day.

CASE 13.—A white man, 53 years of age, was stuporous when he was admitted to the hospital on Sept. 1, 1943. Although it was stated that two years before his blood pressure had been found to be "200+," he had had no symptoms until six months before, when progressive weakness and dyspnea had begun. For three months there had been increasing edema of the legs and some blurring of vision.

The systolic pressure was 240 mm. of mercury and the diastolic 130. Pitting edema was severe in the legs and over the sacrum. There were moist rales at the bases of both lungs and dulness on percussion at the right base. The heart was enlarged, the aortic second sound was accentuated, and a gallop rhythm was heard. The liver was 4 fingerbreadths below the right costal margin, and there was sclerosis, grade 3, of the peripheral arteries. Funduscope examination revealed the retinopathy of malignant hypertension.

The patient's course was marked by rapidly progressive cardiorenal failure, with death on the ninth day after his admission to the hospital.

CASE 14.—When a white man 53 years of age came to the clinic in April 1940 for prostatic resection, his highest blood pressure was 140 mm. of mercury

systolic and 82 diastolic. He returned on Jan. 1, 1944, stating that six months previously he had noted sudden onset of exhaustion, increasing dyspnea on effort and edema of the ankles, severe headaches in the morning, attacks of paroxysmal nocturnal dyspnea and progressive loss of weight. One month previously, because his vision suddenly blurred, he went to a physician, who found his blood pressure "250." He had vomited each morning for four days.

The patient was ashen, anxious and sickly looking. There was considerable enlargement of the heart and the aortic second sound was greatly accentuated. A few moist rales were heard at the bases of the lungs. The optic fundi showed the retinopathy of malignant hypertension.

The patient's course was marked by progressive cardiorenal failure with increasing weakness, Cheyne-Stokes breathing and pulmonary edema. He died fourteen days after his admission to the hospital.

CASE 15.—A white man, 43 years of age, came to the clinic on Dec. 10, 1943. In the previous year he had lost 22 pounds (10 Kg.) but otherwise felt well until five weeks before coming to the clinic, when he noted painless hematuria, dyspnea on effort, severe headaches in the morning and aching lumbar pain. For two weeks his vision had been failing, and he had had some swelling of the ankles and, for the same period, aching in the right groin and testicle.

The systolic blood pressure was 205 mm. of mercury and the diastolic 135. There was considerable tortuosity of the temporal arteries. The heart was enlarged to the left. Examination with the funduscope revealed the retinopathy of malignant hypertension. When a simple roentgenogram of the abdomen showed calculi in the left kidney, an excretory urogram was attempted. Neither kidney excreted the dye in visible amounts.

Twelve hours after this procedure, the patient suddenly passed into a coma. It was the opinion of a neurologist that the patient had had a cerebral hemorrhage. He died two days later.

CARDIAC MUSCLE

Further Studies; Investigation of Chemical Changes in Myocardial Insufficiency with
Special Reference to Adenosinetriphosphate

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DURING the past decade chemical studies have been made on the human heart by workers from several laboratories in an effort to correlate heart failure with known facts of muscle chemistry. From these studies has come a consistent agreement among all published data that creatine is usually decreased in the failing heart. Total phosphorus and acid-soluble phosphorus have likewise been found to be decreased,¹ and most workers have found a lowered potassium.

To investigate further the chemical changes associated with myocardial insufficiency, Mangun and Roberts² studied acid-soluble phosphorus compounds of the dog's heart in aortic insufficiency. No losses were observed in the early stages, but in 2 dogs allowed to progress into the late stages of cardiac failure (approximately one year later) a marked decrease was noted in the adenosinetriphosphate and phosphocreatine content of the left ventricle. These findings made it desirable to investigate the adenosine compounds present in the failing

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A preliminary report of this work was presented before the American Society of Biological Chemists, 1940. Mangun, G. H., and Myers V. C.: Purine Content of Human Cardiac and Voluntary Muscle, *J. Biol. Chem.* **133**:1xii, 1940.

1. (a) Wilkins, W. E., and Cullen, G. E.: Electrolytes in Human Tissue: A Comparison of Normal Hearts with Hearts Showing Congestive Heart Failure, *J. Clin. Investigation* **12**:1063, 1933. (b) Decherd, G. M., Jr., and Blum, G. E., Jr.: Phosphorus Fractions in Human Heart Muscle, *Proc. Soc. Exper. Biol. & Med.* **38**:341, 1938. (c) Mangun, G. H.; Reichle, H. S., and Myers, V. C.: Further Studies on Human Cardiac and Voluntary Muscle: Possible Implications of Changes in the Creatine, Phosphorus and Potassium Content with Special Reference to Heart Disease, *Arch. Int. Med.* **67**:320 (Feb.) 1941. (d) Herrmann, G., and Decherd, G. M., Jr.: The Chemical Nature of Heart Failure, *Ann. Int. Med.* **12**:1233, 1939.

2. Mangun, G. H., and Roberts, J. T.: Unpublished observations.

human heart. Since adenosinetriphosphate and related compounds break down rapidly after death, it was necessary to devise a technic suitable for the estimation of total acid-soluble purines in such tissues.

Several methods were studied, but only one proved to possess suitable characteristics of specificity, accuracy and sensitivity to warrant use with small samples of tissue. The method consists essentially in the precipitation of purines in a hydrolyzed trichloroacetic acid extract of tissue with copper bisulfite and the estimation of the nitrogen content of the precipitate. Since the purines present are undergoing varying degrees of deamination to oxypurines, it is also necessary to convert unchanged amino purines to oxypurines. Nitrous acid deamination was employed for this purpose. The final method as used in the present series of determinations is as follows:

METHOD

For the determination of oxypurine nitrogen a sample of tissue weighing about 1 Gm. is transferred to a mortar and ground with ten times its weight of 5 per cent trichloroacetic acid, washed and filtered. An aliquot of the filtrate containing not less than 0.2 mg. of nitrogen (10 cc. or more) is transferred to a conical centrifuge tube. Enough ten times normal sulfuric acid is added to make the solution normal, and this is followed by 2 to 3 drops of 1:2 solution of sodium nitrite. The solution is placed in a boiling water bath for one hour to remove the trichloroacetic acid and excess nitrous acid, after which it is cooled, and a drop of phenolphthalein added and neutralized with sodium hydroxide to a faint pink. It is then replaced in the boiling water bath, and 0.4 cc. of saturated solution of sodium bisulfite is added, followed by 0.6 cc. of 10 per cent solution of copper sulfate for each 10 cc. of solution. Heating is continued for several minutes until the precipitate becomes dark brown. It is then cooled and centrifuged. The precipitate is washed with 2 cc. portions of boiling water, the precipitate being broken with a stirring rod and centrifuged after each washing. The nitrogen content of the precipitate is now determined by the micro-Kjeldahl method of Kerr.³ If total extractive purine nitrogen is desired, addition of sodium nitrite is omitted. Other determinations were carried out as described in an earlier paper.^{1c}

In our earlier studies on normal and pathologic human hearts a large number of the calculations were also made on dry fat-free tissue. Some added information may be secured in this way, but significant changes were always evident in the analyses calculated on a wet basis. On this account the analyses given in the present paper are reported only on a wet basis.

RESULTS OF EXPERIMENTS

The recovery of oxypurine nitrogen from known solutions and after addition to trichloroacetic acid extracts of muscle is shown in table 1. The data demonstrate that complete conversion of amino purine to oxy-

3. Kerr, S. E.: The Determination of Purine Nucleotides and Nucleosides in Blood and Tissues, *J. Biol. Chem.* **132**:147, 1940.

purines has been obtained with nitrous acid without loss of oxypurine and that quantitative recoveries of added purines are obtained in tissue extracts.

The effects of autolysis on the purine content of cardiac muscle are shown in table 2. Essentially no change in oxypurine nitrogen occurs in samples at 3 to 5 C. for forty-eight hours although there is a progressive decrease in the total purine nitrogen during the first twenty-four hours to a value only slightly higher than the oxypurine content.

TABLE 1.—*Recovery of Oxypurines from Pure Solutions and Trichloroacetic Acid Extracts of Muscle (Average of Triplicate Determinations)*

Purine Added	Oxypurine Nitrogen in Original Sample, Mg.	Oxypurine Added, Mg.	Total Oxypurine Found, Mg.	Recovery, Percentage
Adenine.....	0	0.357	0.355	99.5
Hypoxanthine.....	0	0.496	0.497	100.2
Guanine.....	0	0.459	0.465	101.1
Xanthine.....	0	0.384	0.386	99.6
Adenine added to skeletal muscle extract...	0.338	0.143	0.478	99.4
Adenine added to human heart extract....	0.191	0.143	0.339	101.8
Adenine added to dog heart extract.....	0.172	0.143	0.314	99.4

TABLE 2.—*The Effect of Autolysis on Cardiac Muscle Purine Nitrogen* (Mg. of Purine Nitrogen per Hundred Grams of Muscle)*

Purines Determined	Hours Post Mortem			
	2 Hr.	12 Hr.	24 Hr.	48 Hr.
Total extractive purine nitrogen.....	41.2	37.1	36.5	36.8
Oxypurine nitrogen.....	34.4	35.1	33.9	34.7

* Stored in icebox at 3 to 5 C.

TABLE 3.—*Average Purine Nitrogen Content of Human Cardiac and Voluntary Muscle in Ten Cases (Mg. per Hundred Grams of Muscle)*

	Total Extractive Purine Nitrogen	Oxypurine Nitrogen	Amino Nitrogen
Left ventricle.....	38.0	34.5	3.5
Right ventricle.....	25.2	22.3	2.9
Pectoralis major.....	34.3	31.1	3.2

Data on 10 miscellaneous cases in which both total extractive purine nitrogen and oxypurine nitrogen were determined in the left and the right ventricle and the pectoralis major are presented in table 3. In most cases it was found that about half of the total purines were deaminized. For individual cases this ranged from 35 to 85 per cent, if all nitrogen lost by treatment with nitrous acid is assumed to arise from the deamination of adenine.

Analytic observations at necropsy in a series of 24 cases, in which oxypurine nitrogen, creatine and total acid-soluble phosphorus were determined, are summarized in table 4. The following deductions seem warranted:

The adenine content (calculated on the basis of oxypurine nitrogen) of the left ventricle bears the same approximate relationship as the creatine and phosphorus content and are probably due to the same cause, namely, a relatively higher percentage of muscle tissue in the left ventricle per unit weight of tissue.

The adenine content of voluntary muscle is approximately the same as that of the left ventricle. Creatine, however, is nearly twice as high in voluntary muscle as it is in the myocardium of the left ventricle.

In 5 of 6 cases of myocardial insufficiency, the purine content of the left ventricle was lower than that observed in the 18 remaining cases in which death was attributed to other causes. In the 1 case in which the

TABLE 4.—*Average Oxypurine Nitrogen (Calculated as Adenine), Creatine and Total Acid-Soluble Phosphorus Content of Human Cardiac and Voluntary Muscle in Different Conditions (Mg. per Hundred Grams)*

	No. of Cases	Left Ventricle			Right Ventricle			Pectoralis Major		
		Adenine	Creatine	Total Acid-Soluble Phosphorus	Adenine	Creatine	Total Acid-Soluble Phosphorus	Adenine	Creatine	Total Acid-Soluble Phosphorus
Entire series.....	24	86	205	106	54	152	74	77	388	148
Heart failure.....	6	72	161	91	54	128	67	71	344	129
Tuberculosis.....	5	87	225	117	56	162	78	74	422	161
Pneumonia.....	8	90	222	110	48	160	75	78	386	145
Miscellaneous.....	5	91	311	107	63	161	78	87	406	163

purine content of the left ventricle was essentially normal, the purine content of the right ventricle was substantially lowered. In some cases of pneumonia, but not all, the right ventricle appears to be chemically deficient. This suggests that the right ventricle may become fatigued in those conditions involving the lungs to such a degree as to cause failure of the right side of the heart. Findings with regard to creatine and total acid-soluble phosphorus are in essential agreement with results previously reported.⁴

COMMENT

The method presented in the paper for the determination of purines was not further investigated for specificity. However, a high degree of

4. Myers, V. C., and Mangun, G. H.: Some Chemical Observations on the Human Heart in Health and Disease, *J. Lab. & Clin. Med.* **26**:199, 1940. Myers, V. C.: Some Chemical Changes in the Myocardium Accompanying Heart Failure, *Bull. New York Acad. Med.* **18**:303, 1942.

specificity has previously been demonstrated for the copper bisulfite method of purine precipitation.⁵ It was noted that when the nitrous acid deamination was applied to tissue extracts, autolysis resulted in no change in oxypurine nitrogen within forty-eight hours after death. In the absence of nitrous acid, the total purine nitrogen decreased during the first twelve hours to a value of approximately 2 mg. per hundred grams higher than the oxypurine value, and dropped no further within the forty-eight hour observation period. This may be due to the precipitation of a small amount of some other nitrogenous compound which is destroyed by treatment with nitrous acid.

It is probable, but not proved, that most of the acid-extractable purines found in muscle tissue originate from the hydrolysis of adenosinetriphosphoric acid and related compounds.

A recent report by Stoner and Green⁶ indicates that tissue damage releases adenosine compounds sufficiently to cause a noticeable rise in the adenosine equivalent of the blood. This fact may be related to the decreases in purines observed in the heart in myocardial insufficiency.

A recent paper by Palladin⁷ on the biochemistry of muscle training summarizes the results of a series of studies on the effects of muscle training and fatigue on voluntary muscle. The Kiev group demonstrated that training increased the concentrations of various muscle constituents believed to be intimately associated with transfer of muscle energy and with cell respiration, while fatigue adversely affected the untrained muscle tissue to a far greater degree than the trained. It is probable that our observations on the heart are fundamentally related to the same phenomena and that the changes observed are directly related to a decrease in the chemical efficiency of the heart arising either from fatigue due to overwork or from tissue anoxia, as suggested by Wearn.⁸

The observations of the Kiev group on the poor results of training in animals on vitamin C-free and on thiamine-free diets also emphasize a point of both practical and theoretic significance—that unless favorable nutritional conditions are created, the ability of muscle to withstand fatigue and to respond to increased energy demands is poor.

5. Hitchings, G. H., and Fiske, C. H.: The Determination of the Purines, *J. Biol. Chem.* **140**:491, 1941.

6. Stoner, H. B., and Green, H. N.: Further Observations on the Adenosine Equivalent of the Blood of Rabbits Following Lethal Forms of Tissue Injury, *J. Path. & Bact.* **57**:337, 1945.

7. Palladin, A. V.: The Biochemistry of Muscle Training, *Science* **102**:576, 1945.

8. Wearn, J. T.: Morphological and Functional Alterations of the Coronary Circulation, *Bull. New York Acad. Med.* **17**:754, 1941.

SUMMARY

A method is presented for the estimation of total acid-soluble purines and of oxypurines in biologic material which involves hydrolysis of purine compounds, deamination with nitrous acid, precipitation with copper bisulfite and estimation of the nitrogen content of the precipitate.

The acid-extractable purine content of the left ventricle, calculated as adenine, is decreased in myocardial insufficiency. Lowered concentrations of purine were also observed in the myocardium of the right ventricle in some, but not all, cases of pneumonia.

Progress in Internal Medicine

INFECTIOUS DISEASES

Twelfth Annual Review of Significant Publications

HOBART A. REIMANN, M.D.

PHILADELPHIA

THE RESULTS of continued research on antibiotic agents and their practical application hold the chief interest in the field of infectious diseases. Much knowledge has accrued concerning the value of penicillin, streptomycin and other agents when used in the treatment of certain infections and their lack of effect when used in the treatment of others. Intensive investigation of the chemical structure of antibiotics and development of better methods for their commercial production are in progress. The use of penicillin to combat many serious infections, such as the bacterial pneumonias, infections with hemolytic streptococci and subacute bacterial endocarditis, has brought about a great reduction in their incidence and mortality rate. The mortality from degenerative cardiac, renal and other diseases has also declined as a result of the control of incidental infections, which commonly cause death in such patients.¹ This decline, however, has been continuous for many years. No doubt it has been speeded by modern methods of prevention and treatment. Further reduction of the incidence and the mortality rate of chronic cardiovascular-renal and other degenerative diseases may be anticipated in the future from the present control of certain infections which give rise to such diseases.

Many advances in knowledge have come from extensive investigation of diseases affecting the armed forces, particularly epidemic infections of the respiratory tract, hepatitis, malaria and exotic diseases. There have also been alarming developments pertaining to the possibilities of future biologic warfare. Although assurance was given in 1943² that there were insurmountable difficulties in the way of the successful use of infectious agents as offensive weapons, it now is evident that confidence was not actually so great.³ While biologic warfare is still

From the Jefferson Medical College and Hospital.

1. Large Decline in Mortality from Degenerative Diseases, *Statist. Bull. Metrop. Life Insur. Co.* **27**:5-8 (March) 1946.

2. Feasibility of Bacterial Warfare, editorial, *J. A. M. A.* **122**:810-811 (July 17) 1943.

3. Biologic Warfare, editorial, *J. A. M. A.* **130**:349 (Feb. 9) 1946.

largely theoretic, since no practical application has been made, secret but active investigation on a large scale has been conducted to forestall any surprise attacks and to develop protective and aggressive measures with respect to contagious diseases of animals, plants and man. The organization of the project and its objectives are described by Merck.⁴

PENICILLIN

Although the commercial output of penicillin has increased to 1.5 trillion units a month, it is only recently that domestic demand has been exceeded.⁵ Despite the large supply, there were several periods during the winter when it fell short of the demand. A large amount of penicillin is wasted, and its more judicious use would do much to prevent a shortage. A committee in New York warned that penicillin should not be used for the prophylaxis and the treatment of diseases for which it is of no value, that treatment of patients should not be continued long after any effect may be expected and that oral administration of the drug should not be practiced since it requires a several-fold increase of dosage.⁶ Doses giving optimal amounts in the blood are all that is needed; larger doses merely raise the amount without increasing antibacterial activity.⁷ The application of silly trade names to penicillin was deprecated editorially.⁸ Interesting reviews of the development of antibiotics were made by Florey⁹ and by Molitor.¹⁰ Research on antibiotics has gone on for seventy years, and the word "antibiosis" was coined in 1889.

Certain information concerning penicillin withheld during the war is now released.¹¹ Commercial penicillin is not a single substance but a mixture of at least four chemical types of penicillin designated as G, X, F and K, which appear in varying combination and proportion, depending on the strain of *Penicillium* used for harvest, on the method of preparation and on other factors. Prior to 1944 penicillin was composed

4. Merck, G. W.: Biological Welfare, *Mil. Surgeon* **98**:237-242 (March) 1946.

5. Production of Penicillin High Enough to Permit Export, Washington Letter, *J. A. M. A.* **131**:1009 (July 20) 1946.

6. Penicillin Therapy, Current Comment, *J. A. M. A.* **130**:414 (Feb. 16) 1946.

7. Rammelkamp, C. H., and Kirby, W. M. M.: Factors Determining the Dosage of Penicillin in the Treatment of Infections, *Bull. New York Acad. Med.* **21**:656-672 (Dec.) 1945.

8. Silly Names for Penicillin Products, editorial, *J. A. M. A.* **130**:279 (Feb. 2) 1946.

9. Florey, H. W.: The Use of Microorganisms for Therapeutic Purposes, *Brit. M. J.* **2**:635-642 (Nov. 10) 1945.

10. Molitor, H.: Bacterial Chemotherapy, *Federation Proc.* **5**:303-312 (June) 1946.

11. The Changing Character of Commercial Penicillin, Committee on Medical Research, the United States Public Health Service, and the Food and Drug Administration, *J. A. M. A.* **131**:271-275 (May 25) 1946.

chiefly of penicillin G or a mixture of G and F. Later, the G fraction diminished as the F and K fractions increased. It is probable that during the past three years penicillin X has been present only in a small amount. The significance of these changes lies in the fact that K penicillin is unstable, is relatively ineffective in certain infections and reduces curative power.¹² This may account partly for the apparent diminution of the rate of cures of syphilis since May 1944. Strains of group A hemolytic streptococci, pneumococci, gonococci and meningococci are from two to eight times more sensitive to penicillin X than to penicillin G.¹³ Penicillin X is not absorbed as well as the G fraction when given orally.¹⁴ A further complicating factor is the production of increasingly "pure" penicillin by the elimination of certain "impurities" which may also have therapeutic value. Penicillin as now distributed is said to contain about 95 per cent penicillin G.

Miller and Boor¹⁵ supplement their earlier work to show that penicillin not only inhibits growth but also neutralizes the endotoxin of meningococci and gonococci. Miller and Bohnhoff¹⁶ also demonstrated that meningococci developed resistance to penicillin while still retaining their virulence. A curious result was obtained by Carpenter and co-workers¹⁷: Gonococci, as would be expected, developed resistance while growing in mediums containing sulfathiazole, Rivanol (2-ethoxy-6,9-diamino-acridine lactate), Promin (sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate) and penicillin separately. But when mediums containing the first three drugs together were used, only slight resistance developed to each, and when penicillin was added to the combination, no resistance developed to any of the agents. Penicillin obviously played the most important role, probably by preventing growth during which resistance to the other drugs develops. It is hoped that a prediction made recently will not be fulfilled, namely, that owing to the wide and uncontrolled use of penicillin and the gradual

12. Coghill, R. D.; Osterberg, A. E., and Hazel, G. R.: The Relative Effectiveness of Pure Penicillin G, X and K, *Science* **103**:709-710 (June 14) 1946.

13. Ory, E. M.; Meads, M., and Finland, M.: Penicillin X, *J. A. M. A.* **129**:257-261 (Sept. 22) 1945.

14. Meads, M.; Ory, E. M., and Finland, M.: Oral Penicillin X, *Science* **103**:501-502 (April 26) 1946.

15. Miller, C. P., and Boor, A. K.: Protection of Mice Against Lethal Action of Gonococcal Endotoxin by Penicillin, *Proc. Soc. Exper. Biol. & Med.* **61**:18-20 (Jan.) 1946.

16. Miller, C. P., and Bohnhoff, M.: Studies on the Action of Penicillin: V. Virulence of Penicillin Resistant Strains of Meningococcus, *Proc. Soc. Exper. Biol. & Med.* **60**:356-357 (Dec.) 1945.

17. Carpenter, C. M., and others: Adaptability of Gonococcus to Four Bacteriostatic Agents, Sodium Sulfathiazole, Rivanol Lactate, Promin and Penicillin, *Proc. Soc. Exper. Biol. & Med.* **60**:168-171 (Oct.) 1945.

development of resistance generally among bacteria, penicillin as now prepared will eventually cease to be of value in the treatment of disease.¹⁰

Oral Therapy.—Penicillin given orally in about five times the usual parenteral dose accumulates in the blood in amounts large enough to control infections caused by gonococci, hemolytic streptococci and pneumococci but probably not those caused by staphylococci and meningococci, or subacute bacterial endocarditis.¹⁸ For initiating treatment of any severe infection and for treatment in which large doses over a long period are essential, the parenteral route is preferable. Penicillin was just as satisfactory when given in capsules or dissolved in water as when administered in various combinations with buffer substances. The amount of penicillin in the blood was often greater in patients with pneumonia than in normal persons given similar amounts. Most patients with gonorrhea were cured with a daily dose of 450,000 units, given orally in divided doses, but the response was not quite so good as after full intramuscular dosage.

Pneumococcic pneumonia was satisfactorily treated¹⁸ with an initial oral dose of 300,000 units and doses of 100,000 units every two hours thereafter until the temperature remained normal for forty-eight hours. The total dose varied between 2,500,000 and 8,500,000 units. In another group,¹⁹ of 45 patients, only 1 death occurred. They received 200,000 units as an initial dose, followed by 50,000 units every two hours until twenty-four hours after the crisis, when the same dosage was maintained only from 8 a. m. to 10 p. m. The total doses were 750,000 units on the first day and 400,000 to 600,000 units on subsequent febrile days. Treatment usually lasted from four to seven days. In 36 patients a slight secondary rise of fever occurred during the second or the third day of treatment, but there was no evidence that a relapse had occurred. The resumption of therapy caused prompt improvement. Oral therapy in general is as effective as parenteral therapy. Oral therapy was also good in children with gonococcic vaginitis and in those with pneumonia²⁰ when 100,000 units was given in a capsule every three hours. No toxic symptoms resulted.

Hemolytic Streptococcic Infection.—In the experience of Meads's group,²¹ if penicillin is administered parenterally early in scarlet fever and

18. Finland, M.; Meads, M., and Ory, E. M.: Oral Penicillin, J. A. M. A. **129**:315-320 (Sept. 29) 1945.

19. Bunn, P. A.; McDermott, W.; Hadley, S. J., and Carter, A. C.: The Treatment of Pneumococcic Pneumonia with Orally Administered Penicillin, J. A. M. A. **129**:320-327 (Sept. 29) 1945.

20. Ross, S.; Burke, F. G., and McLendon, P. A.: Penicillin by Mouth, J. A. M. A. **129**:327-332 (Sept. 29) 1945.

21. Meads, M., and others: Penicillin Treatment of Scarlet Fever, J. A. M. A. **129**:785-789 (Nov. 17) 1945.

treatment continued for seven days the carrier state may be eliminated and complications caused by hemolytic streptococci prevented; but the eruptive and toxic manifestations are not influenced. Another group²² recommends that 480,000 units be given over an eight day period. Penicillin was successful in controlling scarlet fever caused by sulfonamide-fast type 17 and 19 of hemolytic streptococci. Ashley's results were similar, but he gave an injection of 50 cc. or more of human convalescent serum in addition.²³

In the treatment of pharyngitis caused by hemolytic streptococci, penicillin given parenterally shortened the disease from 4.9 days in the untreated to 3.1 days in those treated.²⁴ The carrier state persisted for a week after penicillin therapy in 30 per cent of those who were treated and in all those who were untreated. Oral therapy was also effective. Spink's group²⁵ reports similar favorable results. Daily intramuscular injection of more than 200,000 units was needed to eliminate hemolytic streptococci from the throat more than temporarily. Penicillin did not prevent subsequent attacks of rheumatic fever. The question of the development of penicillin-fast strains of hemolytic streptococci arises, but no strains significantly resistant to penicillin were encountered.

In another study, penicillin in beeswax-peanut oil mixture injected once a day for five to seven days promptly and permanently eradicated hemolytic streptococci from the nose and the throat in 50 per cent of carriers.²⁶ In the other half the streptococci were reduced by 98 per cent, but relapse of the carrier state took place when treatment was stopped.

A high percentage of patients with empyema caused by hemolytic streptococci, pneumococci or staphylococci recovered without operation after being treated with penicillin.²⁷

Diphtheria Carriers.—In one study²⁸ carriers were not freed of diphtheria bacilli by intramuscular injections of penicillin, but 23 of 31

22. Observations on the Treatment of Scarlet Fever with Penicillin, Epidemiology Unit no. 82, Am. J. M. Sc. **211**:417-420 (April) 1946.

23. Ashley, P.: The Treatment of Scarlet Fever, J. A. M. A. **130**:771-774 (March 23) 1946.

24. Keith, J. D., and others: Penicillin in Hemolytic Streptococcal Infections of the Throat, Canad. M. A. J. **53**:471-477 (Nov.) 1945.

25. Spink, W. W., and others: Sulfadiazine and Penicillin for Hemolytic Streptococcus Infections of the Upper Respiratory Tract, Arch. Int. Med. **77**: 260-294 (March) 1946.

26. Hamburger, M., and Lemon, H. M.: The Problem of the Dangerous Carrier of Hemolytic Streptococci, J. A. M. A. **130**:836-841 (March 30) 1946.

27. Brown, B., and others: Penicillin Treatment of Empyema: Report of Twenty-Four Cases and Review of the Literature, Ann. Int. Med. **24**:343-370 (March) 1946.

28. Kocher, R. A., and Siemsen, W. J.: Diphtheria Carriers Treated with Penicillin, Ann. Int. Med. **24**:883-886 (May) 1946.

persons were cleared when penicillin was given as lozenges or as a nasal spray. In carriers resistant to this form of treatment, tonsillectomy was said to result in negative cultures. The results as reported seem encouraging, but limited facilities did not permit accurate identification of the bacilli, and the cultures reported extend only to the tenth day after the beginning of treatment.

On the other hand, nasal inhalation of penicillin had no effect on the state of carrier of virulent diphtheria bacilli in Paull's²⁹ patients. Sixty-four per cent of the strains of diphtheria bacilli were sensitive to penicillin.

An official report³⁰ of a nation-wide study of the effect of penicillin as used in the treatment of 11,589 patients with syphilis has been made. The report and other pertinent ones are discussed in the "Annual Review of Syphilis" in the *Archives of Internal Medicine*.

STREPTOMYCIN

Because of the difficulties in the production of streptomycin, not many reports of its use are available for review. So far the results of the treatment of typhoid and brucellosis,³¹ in which the therapy is theoretically specific, are disappointing. At present streptomycin seems to be of most value when used for certain infections of the urinary tract with gram-negative bacteria, for clearing the intestine temporarily of certain gram-negative bacteria,^{31b} for tularemia,³² for *Haemophilus influenzae* meningitis, for bacteremia with gram-negative bacilli and for certain infections of wounds.³³ Streptomycin was said^{33a} to have

29. Paull, R., and others: Studies on the Sensitivity of Diphtheria to Penicillin, *Ann. Int. Med.* **24**:413-419 (March) 1946.

30. The Treatment of Early Syphilis with Penicillin, Committee on Medical Research and the United States Public Health Service, *J. A. M. A.* **131**:265-271 (May 25) 1946.

31. (a) Herrell, W. E., and Nichols, D. R.: The Clinical Use of Streptomycin: A Study of Forty-Five Cases, *Proc. Staff Meet., Mayo Clin.* **20**:449-462 (Nov. 28) 1945. (b) Reimann, H. A.; Price, A. H., and Elias, W. F.: Streptomycin for Certain Systemic Infections and Its Effect on the Urinary and Fecal Flora, *Arch. Int. Med.* **76**:269-277 (Nov.-Dec.) 1945.

32. (a) Foshay, L., and Pasternack, A. B.: Streptomycin Treatment of Tularemia, *J. A. M. A.* **130**:393-398 (Feb. 16) 1946. (b) Abel, O.: The Use of Streptomycin in Tularemia, *J. Missouri M. A.* **43**:167-169 (March) 1946. (c) Cohen, R. B., and Lasser, R.: Primary Tularemic Pneumonia Treated with Streptomycin, *J. A. M. A.* **131**:1126-1127 (Aug. 3) 1946. (d) Peterson, R. L., and Parker, R. R.: Tularemic Pneumonia: Treatment with Streptomycin, *Pub. Health Rep.* **61**:1231-1234 (Aug. 23) 1946. (e) Howe, C., and others: Streptomycin Treatment in Tularemia, *J. A. M. A.* **132**:195-200 (Sept. 28) 1946.

33. Streptomycin in the Treatment of Infection, Committee on Chemotherapeutics and Other Agents, *J. A. M. A.* **132**:4-11 (Sept. 7); 70-77 (Sept. 14) 1946.

produced an "extremely dramatic" result in a patient who presumably had *H. influenzae* infection of the lung, recovery occurring within eight hours after an intratracheal injection of 50 mg. Aside from the statement that *H. influenzae* was the predominant organism in the sputum, no proof is offered that it caused the disease in this patient or in 2 others in which recovery occurred after intratracheal injection of streptomycin. Furthermore, only slight amounts of streptomycin are absorbed when the drug is given by inhalation. Similar criticism may be applied to the report of successful parenteral treatment of a patient with pneumonia due to Friedländer's bacillus.³⁴ Streptomycin was used successfully for endocarditis caused by streptococci resistant to penicillin^{34a} and by gram-negative bacilli.^{34b} Streptomycin is said to be the most effective agent used to treat experimental tuberculosis in animals,³⁵ but in 34 patients³⁶ it seemed to have only a limited suppressive effect; there was no evidence of effective bactericidal action. Optimism is unwarranted at present. Good results are reported³⁷ from the treatment of an infant with tuberculous meningitis and from that of a patient with tuberculous laryngitis.³⁸ No effect was noted in another patient with meningitis.^{31b} No effects of streptomycin were noted in 10 patients treated for cholera other than a reduction of the number of vibrios in the stools.³⁹ Vibrios from different patients of the same epidemic varied greatly in their resistance to streptomycin. Streptomycin

Nichols, D. R., and Herrell, W. E.: Streptomycin: Its Clinical Use and Limitations, *ibid.* **132**:200-205 (Sept. 28) 1946.

33a. Durant, T. M., and others: Streptomycin Therapy in Hemophilus Influenzae Pulmonary Infections, *J. A. M. A.* **131**:194-196 (May 18) 1946.

34. Bishop, C. A., and Rasmussen, R. F.: Klebsiella Pneumonia Treated with Streptomycin, *J. A. M. A.* **131**:821-822 (July 6) 1946.

34a. Priest, W. S., and McGee, C. J.: Streptomycin in the Treatment of Subacute Bacterial Endocarditis, *J. A. M. A.* **132**:124-126 (Sept. 21) 1946.

34b. Hunter, T. H., and Duane, R. B.: Subacute Bacterial Endocarditis Due to Gram-Negative Organisms, *J. A. M. A.* **132**:209-211 (Sept. 28) 1946.

35. Smith, M. I., and McClosky, W. T.: The Chemotherapeutic Action of Streptomycin and Promine in Experimental Tuberculosis, *Pub. Health Rep.* **60**: 1129-1138 (Sept. 28) 1945.

36. Hinshaw, H. C., and Feldman, W. H.: Streptomycin in Treatment of Clinical Tuberculosis: A Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **20**:313-318 (Sept. 5) 1945.

37. Cooke, R. E.; Dumphy, D. E., and Blake, F. G.: Streptomycin in Tuberculous Meningitis: Reports of Its Use in a One-Year-Old Infant, *Yale J. Biol. & Med.* **18**:221-226 (Jan.) 1946.

38. Figi, F. A.; Hinshaw, H. C., and Feldman, W. H.: Treatment of Tuberculosis of the Larynx with Streptomycin: Report of Case, *Proc. Staff Meet., Mayo Clin.* **21**:127-130 (March 20) 1946.

39. Reimann, H. A., and others: Asiatic Cholera, *Am. J. Trop. Med.* **26**:631-647 (Sept.) 1946.

was effective in controlling experimental infections with *Haemophilus pertussis*⁴⁰ and *Pasteurella pestis*⁴¹ in mice.

The essential features of the pharmacologic behavior of streptomycin, particularly in regard to routes of administration, amounts in the body and excretion as reported previously,^{31b} have been confirmed and extended.³³

Buggs and co-workers⁴³ tested the sensitivity to streptomycin of a variety of bacteria. The majority of strains of *Escherichia coli*, *Proteus vulgaris*, *Aerobacter aerogenes*, staphylococci and streptococci were susceptible to amounts of streptomycin in culture mediums comparable to amounts attained in the body. As in our own study,^{31b} great variations in resistance to streptomycin of a given species of bacterium was found. Certain strains develop resistance to streptomycin. Experience indicates that it is questionable whether the degree of resistance of bacteria in vitro is a reliable guide to the amount needed to gain therapeutic effects in the body.^{31b} Rapid development of resistance occurred in 8 patients, resulting in the failure of treatment.^{43a}

With most interest focused on the effects of streptomycin on gram-negative bacteria, it comes as a surprise to learn that the majority of strains of staphylococci tested were sensitive to as little as 1 microgram of the drug. Alpha and beta hemolytic streptococci were somewhat more resistant. According to Miller and Bohnhoff,⁴⁴ meningococci and pneumococci are sensitive to streptomycin but become resistant to it much more rapidly than to penicillin when grown in mediums containing the respective antibiotic substances. Streptomycin-resistant meningococci and pneumococci were sensitive to penicillin, and penicillin-resistant strains were sensitive to streptomycin. The authors believe that penicillin and streptomycin act in different ways, since resistance to streptomycin builds up more rapidly, and abnormal morphologic changes occur in streptomycin-resistant strains but not in penicillin-resistant

40. Bradford, W. L., and Day, E.: Therapeutic Effect of Streptomycin in Experimental Murine Pertussis, *Proc. Soc. Exper. Biol. & Med.* **60**:324-325 (Dec.) 1945. Hegarty, C. P., and others: In Vitro and in Vivo Activity of Streptomycin Against *Hemophilus Pertussis*, *J. Bact.* **50**:651-660 (Dec.) 1945.

41. Wayson, N. E., and McMahon, M. C.: Plague: Treatment of Experimental Animals with Streptomycin, Sulfadiazine and Sulfapyrazine, *J. Lab. & Clin. Med.* **31**:323-332 (March) 1946. Hornibrook, J. W.: Streptomycin in Experimental Plague, *Pub. Health Rep.* **61**:535-538 (April 12) 1946.

42. Footnote deleted on proof.

43. Buggs, C. W., and others: The In Vitro Action of Streptomycin on Bacteria, *J. A. M. A.* **130**:63-67 (Jan. 12) 1946.

43a. Finland, M., and others: Development of Streptomycin Resistance During Treatment, *J. A. M. A.* **132**:16-21 (Sept. 7) 1946.

44. Miller, C. P., and Bohnhoff, M.: Streptomycin Resistance of Gonococci and Meningococci, *J. A. M. A.* **130**:485-488 (Feb. 23) 1946.

ones. Others⁴⁵ also found that the antibacterial action of streptomycin differs from that of penicillin. In contrast with penicillin, streptomycin inhibits the growth of bacteria less well in good mediums than in poor. Tubercle bacilli may develop resistance of more than a thousandfold when exposed to streptomycin.⁴⁶

Streptomycin failed to inhibit the multiplication of influenza virus in chick embryos.⁴⁷ It is less active than penicillin against experimental syphilis.⁴⁸

New Antibiotic Substances.—Search for other antibiotic substances has led to some unexpected sources. One has been found in *Bacillus* larvae⁴⁹ from honey bee larvae and another in cedar wood.⁵⁰ Both agents inhibit the growth of a wide range of both gram-positive and gram-negative bacteria and of fungi. Bacitracin derived from *Bacillus subtilis*, also inhibitive of pathogenic bacteria, has already been used with success clinically.⁵¹ It may be similar to or identical with the substance studied by Metchnikoff in 1897 and reported on by Ramon as subtiline.⁵² Mycoidin is another product of a mold bactericidal for *Mycobacterium tuberculosis*.⁵³ Parachlorophenol is an effective agent against gram-negative bacteria in wound infections,⁵⁴ and various phenanthrene-related substances—for example, vitamin D, ergosterol, cholesterol and bile salts—have an antibacterial action.⁵⁵

45. Wallace, G. I., and others: Studies on the Mode of Action of Streptomycin: I. Effect of Culture Media, *Proc. Soc. Exper. Biol. & Med.* **60**:127-128 (Oct.) 1945.

46. Youmans, G. P., and others: Increase in Resistance of Tubercle Bacilli to Streptomycin: A Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **21**:126-127 (March 20) 1946.

47. Florman, A. L.; Weiss, A. B., and Council, F. E.: Effect of Large Doses of Streptomycin and Influenza Viruses on Chick Embryos, *Proc. Soc. Exper. Biol. & Med.* **61**:16-18 (Jan.) 1946.

48. Dunham, W. B., and Rake, G.: The Activity of Streptomycin in Experimental Syphilis, *Science* **103**:365 (March 22) 1946.

49. Holst, E. C.: An Antibiotic from a Bee Pathogen, *Science* **102**:593-594 (Dec. 7) 1945.

50. Southham, C. M.: Antibiotic Activity of Extract of Western Red Cedar Heartwood, *Proc. Soc. Exper. Biol. & Med.* **61**:391-396 (April) 1946.

51. Johnson, B. A.; Anker, H., and Meleney, F. L.: Bacitracin: A New Antibiotic Produced by a Member of the *B. Subtilis* Group, *Science* **102**:376-377 (Oct. 12) 1945.

52. A New Antibacterial Substance: Subtiline, *Foreign Letters, J. A. M. A.* **129**:1281 (Dec. 29) 1945.

53. Gerber, I. E., and Gross, M.: Inhibition of Growth of *Mycobacterium Tuberculosis* by a Mold Product: The Effect on Pathogenic Human Tubercle Bacilli, *Science* **103**:167-169 (Feb. 8) 1946.

54. Meleney, F. L., and others: Treatment of Mixed Infections with Penicillin, *J. A. M. A.* **130**:121-124 (Jan. 19) 1946.

INFECTIONS OF THE RESPIRATORY TRACT

Increased interest in the minor infections of the respiratory tract, stimulated no doubt by the modern control and subsequent reduction of the incidence of severe bacterial pneumonias, has led to considerable clarification of the problem. A tentative classification of this group of mild diseases may be made on epidemiologic, clinical and etiologic grounds as follows: (a) the common cold; (b) nonbacterial pharyngitis; (c) grip; (d) viroid, which includes both mild and pneumonic forms caused by the agents of viral pneumonia, and (e) influenza A and B.⁵⁶ Abernethy⁵⁷ reported that diseases resembling the common cold and exudative (nonbacterial) pharyngitis had been transferred separately to volunteers, indicating an etiologic distinction between the two which had long been suspected. It is still uncertain whether grip is a distinct disease or a group of separate unclassifiable entities which will eventually be included under the other headings. At any rate, further progress of knowledge of the infections may be anticipated. The problem is about to be investigated on a large scale at the National Institute of Health and the Western Reserve University School of Medicine in this country and by the Medical Research Council in England.

According to extensive studies⁵⁸ on large groups of soldiers, the ordinary variety of acute infections of the respiratory tract had epidemiologic features distinct from and independent of those of influenza, infections with hemolytic streptococci and rubella, suggesting that they represent either a single entity or a group of similar ones. As was noted in many earlier observations, new recruits are particularly susceptible, and the rapid disappearance of attacks among them suggests the development of immunity. Studies, however, do not support the general impression that the following are the chief factors in the high rate of infection among recruits: (1) exchange of nasopharyngeal flora, (2) exhaustion from unaccustomed duties, (3) reaction to immunization processes, (4) difficulties in psychologic adjustment, (5) unsanitary mess halls or (6) inclement weather. While these may be contributing factors, there is no doubt but that the season of the year is of more

55. Raab, W.: Antibacterial Action of Phenanthrene-Related Substances, *Science* **103**:670-671 (May 31) 1946.

56. Reimann, H. A.: Viral Infections of the Respiratory Tract, *J. A. M. A.* **132**:487-493 (Nov. 2) 1946.

57. Abernethy, T. J.: Experimental Transmission of Minor Respiratory Illness to Human Volunteers, read at the meeting of the American Society of Clinical Investigation, 1946.

58. Acute Respiratory Disease Among New Recruits, Commission on Acute Respiratory Disease, *Am. J. Pub. Health* **36**:439-450 (May) 1946.

importance since, for reasons unknown, epidemics occurred most regularly in the winter and the early spring. Other diseases of the respiratory tract so mild as often to escape detection occur during the summer and the fall.

In the studies of Rantz and associates⁵⁹ infections of the respiratory tract due to undetermined viruses did not favor the spread of hemolytic streptococci. Like others, they found that the stress of introducing troops to a new area led to an increase of infections due to viruses and to hemolytic streptococci regardless of duration of military service.

Gamma globulin injected in 4 to 10 cc. amounts had no effect in preventing attacks of an influenza-like infection of the respiratory tract.⁶⁰

Viral Pneumonias.—The most important contribution in this field is a virus recovered from patients which can be maintained by passage in chick embryos, causes pulmonary lesions in hamsters and cotton rats, is neutralized by convalescent serum and can be differentiated from the psittacosis group of organisms by neutralization tests.⁶¹ Eaton⁶² estimates that the newly discovered virus is the cause of 60 per cent of the incidence of viral pneumonia; less than 20 per cent is caused by the viruses of influenza and the psittacosis group, a small percentage by the viruses of lymphocytic choriomeningitis and Q fever and the rest by causes yet unknown. If 70 to 80 per cent of the incidence of these forms of pneumonia is caused by viruses, there is no further need to use the undesirable term "atypical pneumonia."

The next point to prove is that some of these forms of pneumonia, except for the psittacosis group, are only the severe forms with pulmonary involvement of a widespread mild infection of the respiratory tract as suggested by Reimann in 1938.⁶³ In Minnesota an epidemic of an

59. Rantz, L. A., and others: Streptococcic and Nonstreptococcic Disease of the Respiratory Tract: Epidemiologic Observation, *Arch. Int. Med.* **77**:121-131 (Feb.) 1946.

60. Yannet, H., and Deutsch, J. V.: Gamma Globulin Not Effective in Prophylaxis of Epidemic Respiratory Infections, *J. A. M. A.* **131**:593 (June 15) 1946.

61. Eaton, M. D.; Meiklejohn, G.; van Herick, W., and Corey, M.: Studies on the Etiology of Primary Atypical Pneumonia: II. Properties of the Virus Isolated and Propagated in Chick Embryos, *J. Exper. Med.* **82**:317-328 (Nov.) 1945. Eaton, M. D.; van Herick, W., and Meiklejohn, G.: Studies on the Etiology of Atypical Pneumonia: III. Specific Neutralization of the Virus by Human Serum, *ibid.* **82**:329-342 (Nov.) 1945. Eaton, M. D.: Serological Differentiation of Primary Atypical Pneumonia from Virus Pneumonia of the Psittacosis Group, *Proc. Soc. Exper. Biol. & Med.* **60**:231-235 (Nov.) 1945.

62. Eaton, M. D.: Recent Observations on Virus Pneumonia, California & West. Med. **63**:113-116 (Sept.) 1945.

63. Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia: A Disease Entity Probably Caused by a Filtrable Virus, *J. A. M. A.* **111**:2377-2384 (Dec. 24) 1938. Reimann, H. A., and Havens, W. P.: An Epidemic Disease of the Respiratory Tract, *Arch. Int. Med.* **65**:138-150 (Jan.) 1945.

infection of the respiratory tract affected 191 persons over a two month period; of the 191 attacks, 113 were classified as mild, 47 as moderately severe and 31 as severe, some of these with pneumonia.⁶⁴ Serum from patients with severe attacks and from some with mild ones showed an increase of antibodies which neutralized Eaton's virus, suggesting that they were of the same origin.

Horsfall and Curnen⁶⁵ report the presence of antibodies which neutralize the pneumonitis virus of mice (PVM virus) in rabbits, monkeys, human beings, hamsters, guinea pigs and mice in that order of frequency. The results indicate that PVM virus is widely distributed, even in man. Antibodies to the virus may be stimulated by nonspecific, innocuous measures. Horsfall therefore feels that if specific antibodies develop in animals inoculated with material from patients with viral pneumonia, this means only that their production has been stimulated nonspecifically and does not indicate the passage of the virus. It could be interpreted differently. As mentioned in last year's review, if man, as is now shown, may have had PVM infection, why cannot the virus, which may actually be present, be transmitted to mice? Andrewes⁶⁶ discovered in mice a new virus which causes "grey lungs." Adams⁶⁷ reports a third epidemic of viral pneumonia among infants in Minnesota. It is remarkable that no report of a similar epidemic occurring elsewhere has been made.

Psittacosis-Ornithosis-S-F Group.—Several more agents of this obviously large and ever widening group of infections have been discovered. Two new ones have been added to the list. One in Chicago, called the Illinois virus,⁶⁸ was obtained from 2 patients who died. It was related to, but different from, known viruses of this group. The other one, a virus isolated during an outbreak of a severe form of pneumonia in Louisiana, is apparently also different.⁶⁹ A third agent was found to exist normally in the respiratory tracts of mice; it was more like psittacosis virus than Nigg's mouse pneumonitis virus.⁷⁰ It is even suggested that the agent of heartwater fever of sheep belongs

64. Breslow, L.: Epidemic of Acute Respiratory Disease Associated with Atypical Pneumonia, *J. Clin. Investigation* **24**:775-779 (Nov.) 1945.

65. Horsfall, F. L., Jr., and Curnen, E. C.: Studies on Pneumonia Virus of Mice (PVM), *J. Exper. Med.* **83**:43-64 (Jan.) 1946.

66. Andrewes, C. H., and Glover, R. E.: Grey Lung Virus: An Agent Pathogenic for Mice and Other Rodents, *Brit. J. Exper. Path.* **26**:379-386, 1945.

67. Adams, J. M.: Third Epidemic of Primary Virus Pneumonia Among Infants in Minnesota, *Journal-Lancet* **65**:192-193 (May) 1945.

68. Zichis, J., and Shaughnessy, H. J.: Isolation of an Apparently New Virus from Two Fatal Pneumonia Cases, *Science* **102**:301-302 (Sept. 21) 1945.

69. Larson, C. L., and Olson, B. J.: An Epidemic of Some Pneumonitis in the Bayou Region of Louisiana, *Pub. Health Rep.* **61**:69-78 (Jan. 18) 1946.

in the group; it is now included with the Rickettsias (*R. ruminantium*) but may be more closely related to the psittacosis group.⁷¹ Thus far, the following filtrable but visible agents may be tentatively gathered as a group of related pathogens from human and other sources:

Psittacosis virus (birds and man)	Nigg's mouse pneumonitis virus
S-F virus (man)	Louisiana pneumonitis virus (man?)
Ornithosis virus (birds)	Illinois virus (man)
Ailourosis virus (cats)	Fulmar disease virus (birds, man)
Australian mouse virus	Virus of lymphogranuloma venereum (man)
Meningopneumonitis virus (ferrets, man)	Agent of sheep, heartwater fever

Others, no doubt, remain to be discovered. The pneumonia of Q fever, caused by a filtrable rickettsia, is discussed later.

Adams and associates⁷² describe an epidemic of 350 cases of viral pneumonia which occurred in Naples in 1945, of which 50 were carefully studied. Unusual features in the outbreak were the failure of cold agglutinin to develop in any instance, a positive heterophilic antibody test in 18 cases, in 10 of which splenomegaly, palpable lymph nodes and macules were noted, and a positive cephalin-cholesterol flocculation test in most cases. There were no increases in the number of lymphocytes or the number of monocytes to suggest infectious mononucleosis. Some of the patients had had malaria. The variations from the usual viral pneumonias suggest that a different causative agent may have been operative. Explosive outbreaks of pneumonia caused by the rickettsia of Q fever also occurred among troops in Italy and in Greece, as discussed under "Rickettsial Diseases."

One author⁷³ thinks that rheumatic pneumonia may at times be confused with viral pneumonia. Pathologically, the pulmonary reactions are similar. His patient supposedly had viral pneumonia, but nine months later cardiovalvular disease developed. The pneumonia, he thinks, may have been rheumatic pneumonia.

Numerous other clinical reports on the common forms of viral pneumonia were published during the year without much new data

70. DeBurgh, P.; Jackson, A. V., and Williams, J.: Spontaneous Infection of Laboratory Mice with a Psittacosis-Like Organism, *Australian J. Exper. Biol. & Med.* **23**:106-108 (June) 1945.

71. Rake, G.; Alexander, R., and Hamre, D. M.: The Relationship of the Agent of Heart-Water Fever: *Rickettsia Ruminantium*, *Science* **102**:424-425 (Oct. 26) 1945.

72. Adams, A. B., and others: Primary Atypical Pneumonia, *Brit. M. J.* **1**:227-231 (Feb. 16) 1946.

73. Jensen, C. R.: Non-Suppurative Post-Streptococcic (Rheumatic) Pneumonitis: Pathologic Anatomy and Clinical Differentiation from Primary Atypical Pneumonia, *Arch. Int. Med.* **77**:237-253 (March) 1946.

being added. In one contribution⁷⁴ ulceration of the bronchial tree was described as a complication, but, according to prevailing opinion, complications are rare. Penicillin is of no value in the treatment of viral pneumonia.⁷⁵

Cold agglutination of erythrocytes was discussed in several papers.⁷⁶ The consensus is that cold agglutinin in a titer of 1:40 or more develops late in the majority of cases of viral pneumonia not of the psittacosis group, that it appears in persons who have not been sick recently, probably as a result of symptomless infection, and it often occurs in a titer lower than 1:40 after many other infections.⁷⁷

Influenza.—It is generally agreed that vaccination against influenza A and influenza B confers a degree of immunity, lasting for a variable time. Most studies indicate that there are fewer attacks in those who have been vaccinated than in those who have not. Because of the promising results, more than 5,000,000 doses of vaccine were given to soldiers in 1943-1944 and even more in 1945-1946.⁷⁸ This project is one of the most extensive medical experiments ever performed. The results are not as yet reported. According to Francis and co-workers,⁷⁹ the incidence of influenza B among 600 vaccinated men was 1.15 per cent, compared with 9.9 per cent in 1,100 unvaccinated ones. There is evidence that the immunity may last for a year after vaccination and that refrigerated vaccine is stable for more than a year.⁸⁰ Antibodies were demonstrable in 69 per cent of vaccinated persons for four months and in 66 per cent for a year.

According to Francis and co-workers,⁷⁹ there was continued but shifting prevalence of influenza B over eight months in 1945 before an outbreak large enough to attract attention occurred. Influenza B was

74. Kay, E. B.: Ulcerative Tracheobronchitis Following Atypical Pneumonia, *Arch. Int. Med.* **76**:93-101 (Aug.) 1945.

75. Allison, S. T.: Penicillin in Primary Atypical Pneumonia with Report of Twenty-eight Cases, *U. S. Nav. M. Bull.* **45**:930-932 (Nov.) 1945.

76. Springarn, C. L., and Jones, J. P.: Cold Hemagglutination in Primary Atypical Pneumonia and Other Common Infections, *Arch. Int. Med.* **76**:75-87 (Aug.) 1945.

77. Finland, M.; Peterson, O. L.; Allen, H. E.; Samper, B. A.; Barnes, M. W., and Stone, M. B.: Cold Agglutinins: I. Occurrence of Cold Isohemagglutinin in Various Conditions, *J. Clin. Investigation* **24**:451-457 (July) 1945.

78. New Influenza Vaccine Going to Civilians Next Year, *Washington Letter, J. A. M. A.* **130**:40 (Jan. 5) 1946.

79. Francis, T.; Salk, J. E., and Brace, W. M.: The Protective Effect of Vaccination Against Epidemic Influenza B, *J. A. M. A.* **131**:275-278 (May 25) 1945. Salk, J. E., and Francis, J.: Immunization Against Influenza, *Ann. Int. Med.* **25**:443-452 (Sept.) 1946.

80. Salk, J. E.; Pearson, H. E.; Brown, P. N.; Smyth, C. J., and Francis, T.: Immunization Against Influenza with Observations During an Epidemic of Influenza A One Year After Vaccination, *Am. J. Hyg.* **42**:307-322 (Nov.) 1945.

prevalent for a year in the form of a smoldering epidemic, which without etiologic proof of its identity could have been mistaken for a series of unrelated episodes here and there. The disease was usually mild, but severe forms, with pneumonia, were recognized. Isolated attacks which ordinarily would have been considered to be undifferentiated mild respiratory infections were demonstrated to be influenza B by serologic tests. Similar observations and studies were made by Sigel and co-workers⁸¹ and by Burnet and co-workers⁸² in Australia.

In an explosive outbreak of influenza A in San Antonio, Texas, 28 per cent of 39 patients had roentgenographic evidence of pulmonary involvement.⁸³ The occurrence of viral pneumonia of other origin, nasopharyngitis and pneumococcic pneumonia was uninfluenced by the epidemic. Over a period the relative distribution of cases of the various diseases was: influenza, 25 per cent; lobar pneumonia, 34 per cent; nasopharyngitis, 45 per cent, and viral pneumonia, 13 per cent.

Different strains of influenza A virus when inoculated in human subjects caused disease of different degrees of severity with different periods of incubation.⁸⁴ Epidemics of influenza may be caused by influenza A virus in two to three year cycles and by influenza B virus in four to six year cycles. The dominant factor controlling the occurrence of epidemics seems to be the balance between immune and susceptible persons in the population.⁸⁵

Further evidence of the occurrence of bacterial pneumonias as secondary manifestations of influenza is given in a report of influenza B and type I pneumococcic pneumonia concurrent in a community.⁸⁶

Burnet⁸⁷ adds further support to his view of the different culture phases of influenza viruses. The virus which resides in the body to cause influenza is in the so-called O phase, and as soon as it is trans-

81. Sigel, M. M.; Hart, M. M.; Hobbs, G., and Guthner, B.: Demonstration of Influenza Virus, Type B, in a Recent Outbreak of Upper Respiratory Infection, *Science* **102**:646 (Dec. 21) 1945.

82. Burnet, F. M.; Stone, J. D., and Anderson, S. G.: An Epidemic of Influenza B in Australia, *Lancet* **1**:807-811 (June 1) 1946.

83. Pollard, M.; Kalkstein, M., and Livesay, H. R.: The Influenza Epidemic of 1943-1944 in San Antonio, Texas, *Am. J. Trop. Med.* **26**:141-143 (Jan.) 1946.

84. Henle, W.; Henle, G.; Stokes, J., and Maris, E. P.: Experimental Exposure of Human Subjects to Viruses of Influenza, *J. Immunol.* **52**:145-166 (Feb.) 1946.

85. The Periodicity of Influenza, The Commission on Acute Respiratory Diseases, *Am. J. Hyg.* **43**:29-37 (Jan.) 1946.

86. The Relation Between Epidemics of Acute Bacterial Pneumonia and Influenza, Commission on Acute Respiratory Diseases, and the New York State Department of Health, *Science* **102**:561-563 (Nov. 30) 1945.

87. Burnet, F. M., and Stone, J. D.: The Significance of Primary Isolation of Influenza Virus by Inoculation of Mice or of the Allantoic Cavity of Chick Embryos, *Australian J. Exper. Biol. & Med.* **23**:147-150 (June) 1945.

ferred to animal hosts, it transforms into the D phase. Virus in the O phase cannot invade mice until it changes into the D phase.

Adams and associates⁸⁸ examined smears from the pharynxes of patients with influenza A. Characteristically there were large sheets of sloughed-off epithelial cells and an exudate composed mainly of mononuclear cells. The latter is characteristic of other viral infections as well, but the procedure may be used to differentiate viral infections of the pharynx from bacterial or fungous infections, in which the exudate is predominantly of polymorphonuclear cells.

Sulfonamide Compounds Used for Prophylaxis.—The enthusiasm incident to the reports that sulfonamide compounds had been used to prevent infections of the respiratory tract in numerous military groups in the past few years must be tempered by the fulfilment of certain predicted consequences. Sulfadiazine suppressed infections with hemolytic streptococci for a time among naval personnel, but during the experiment hemolytic streptococci of types 17 and 19 were sulfonamide resistant, or became so, and gave rise to a serious epidemic.⁸⁹ Sulfadiazine prophylaxis even seemed to increase susceptibility to infection, especially to scarlet fever. A similar experience is reported by Damrosch.⁹⁰ Sulfadiazine gave no worth while benefit in an outbreak of sore throat caused by type 5 hemolytic streptococci from food poisoning.⁹¹

Other studies⁹² showed that sulfadiazine and sulfathiazole not only failed to shorten severe attacks of sore throat due to hemolytic streptococci, but seemed to harm the patient; treated patients did not feel as well on the tenth day as many untreated ones did on the fifth. Spink's group²⁵ reports similar results.

In a further report of studies⁹³ on the prevention of air-borne infections, the oiling of bedding and of floors with Triton oil emulsion (T-13) was successful in reducing the amount of dust and pathogenic

88. Adams, J. M.; Pennoyer, M. M., and Whiting, A. M.: Pathologic Study of the Acutely Inflamed Human Pharynx in Influenza A Infections, *Am. J. Dis. Child.* **71**:162-170 (Feb.) 1946.

89. Sulfadiazine Resistant Strains of Beta Hemolytic Streptococci, Epidemiologic Unit no. 22, *J. A. M. A.* **129**:921-927 (Dec. 1) 1945.

90. Damrosch, D. S.: Chemoprophylaxis and Sulfonamide Resistant Streptococci, *J. A. M. A.* **130**:124-128 (Jan. 19) 1946.

91. A Study of Foodborne Epidemic of Tonsillitis and Pharyngitis Due to B. Hemolytic Streptococcus, Type 5, Commission on Acute Respiratory Diseases, *Bull. Johns Hopkins Hosp.* **77**:143-210 (Sept.) 1945.

92. Clodfelter, H. M.: Treatment of Severe Acute Tonsillitis With and Without Sulfonamides, *Ohio State M. J.* **41**:819-820 (Sept.) 1945.

93. Loosli, C. G., and others: Oil Treatment of Bedclothes for the Control of Dust-Borne Infection: II. Use of Triton Oil Emulsion (T-13) as a Routine Laundry Procedure, *Am. J. Hyg.* **43**:105-115 (March) 1946.

agents in the air of barracks. The measure promises to be of aid in the reduction of air-borne infections in crowded rooms.

Prevention of Pneumococcic Pneumonia.—In a well controlled study, MacLeod and his group⁹⁴ were able to demonstrate the effectiveness of polysaccharides of pneumococci used as specific vaccines against pneumococcic pneumonia. Solutions containing the capsular substances of pneumococci of types I, II, V and VII were used to immunize a population in which pneumonias of these types and also of types XII and IV had been prevalent. Pneumonias caused by pneumococci of the same types which were used for immunization were greatly reduced, while the numbers of infections with types XII and IV were about the same as in preceding years. There was a reduction of pneumonias of types I, II, V and VII even among nonvaccinated persons, suggesting that the reduction of attacks among those who were vaccinated reduced the carrier rate and lessened the general dispersion of these types, with subsequent reduction of contagion.

Phagocytosis of a pneumococcus depends not only on the presence of specific antibody or an injury of the capsule of the pneumococcus but also on certain nonspecific surface phenomena which aid in recovery from infection.⁹⁵

Another case of pneumonia was diagnosed as due to *Streptococcus viridans* infection because this bacterium was found in smears and cultures of the sputum in "pure" growth.⁹⁶ The number of leukocytes was normal, and the disease described seemed to represent viral pneumonia, with which the author says streptococcic pneumonia is usually confused. It is doubtful if *Str. viridans* ever causes pneumonia or that penicillin cured the disease in question. The author does not report any attempt to compare the streptococcus recovered with streptococcus MG or 344, believed by some investigators to be associated with viral pneumonias. The author also perpetuates a curious descriptive error in stating that "prune juice" sputum occurs in pneumonia. Sputum resembling the thin brown juice of prunes rarely if ever occurs in pneumonia.

Another doubtful case was reported, in which the patient was a 7 month old infant.⁹⁷

94. MacLeod, C. M., and others: Prevention of Pneumococcal Pneumonia by Immunization with Specific Capsular Polysaccharides, *J. Exper. Med.* **82**:445-465 (Dec.) 1945.

95. Wood, W. B.; Smith, M. R., and Watson, B.: Surface Phagocytosis: Its Relation to the Mechanism of Recovery in Pneumococcal Pneumonia, *Science* **104**: 28-29 (July 12) 1946.

96. Solomon, S.: Case of *Streptococcus Viridans* Pneumonia Successfully Treated with Penicillin, *Am. J. M. Sc.* **210**:431-435 (Oct.) 1945.

97. Reinhart, J. B., and Venning, W. L.: Pneumonia Due to *Streptococcus Viridans*, *J. Pediat.* **27**:480-483 (Nov.) 1945.

DISEASES CAUSED BY VIRUSES

Poliomyelitis.—After years of study and controversy, the epidemiology of poliomyelitis seems to be greatly clarified. It has been uncertain whether the virus leaves the patient or the carrier chiefly by way of the feces, the oropharyngeal secretions or the blood; whether the infection is water borne, food borne or air borne or is transmitted by insects or by direct contact and whether the route of entry is the gastrointestinal tract, the respiratory tract or insect punctures of the skin. Each view has its proponents, and it is probable that most of them are partly correct. It is probable that various factors play a role. The problem is to determine which ones are the most important. Several studies cast light on the matter.

Casey's group⁹⁸ made a survey of poliomyelitis in Chicago in a nonepidemic year. The disease was apparently highly contagious among children less than 3½ years old, in whom the morbidity rate was 90 per cent. Multiple occurrences of the disease in a family were the rule, but since less than 1 of 6 patients became paralyzed, the majority of attacks were not recognized as those of poliomyelitis unless special diagnostic tests were made. Patient to patient contact seemed to be the most important mode of transmission. There was no evidence that flies played a major role, once the epidemic began.

Observations along similar lines were made in Buffalo on an epidemic which at first thought would have been regarded as an "original" or an isolated outbreak. Attention was directed to the outbreak by the development of paralysis in a patient who in the absence of further information may have been wrongly considered as the source of infection. A study by Smith's group⁹⁹ showed that other patients with undiagnosed mild attacks were present in the community at the same time and had been for some time before. Poliomyelitis had occurred in the community apparently sporadically for at least five months, and the virus had survived and passed unrecognized through a chain of patients with non-paralytic attacks until one with paralysis attracted attention during a small epidemic. Person to person contact was thought to account for the perpetuation of the disease.

Brown and co-workers¹⁰⁰ studied an outbreak in a summer camp. The virus was found in the feces of 5 of 6 cabin mates of a patient in

98. Casey, A. E.; Fishbein, W. I., and Bundesen, H. N.: Transmission of Poliomyelitis by Patient to Patient Contact, J. A. M. A. **129**:1141-1145 (Dec. 22) 1945.

99. Smith, M. L.; Bridge, E. M.; Underwood, H. E., and Dale, G. E.: A Study of the Origin of an Epidemic of Poliomyelitis, J. A. M. A. **127**:1150-1156 (Dec. 22) 1945.

100. Brown, G. C.; Francis T., and Pearson, H. E.: Rapid Development of Carrier State and Detection of Poliomyelitis Virus, J. A. M. A. **129**:121-123 (Sept. 8) 1945.

whom poliomyelitis developed during a period of six days of contact. In one of the carriers poliomyelitis developed nineteen days after his feces were found to harbor the virus. The virus was present in the patient's pharynx during the disease. It may be recalled from previous studies that the virus was recovered from the oropharynx early in the disease in 50 per cent of the cases. The presence of the virus in the stool, however, does not constitute evidence that it entered through the respiratory tract or the gastrointestinal tract, since Melnick¹⁰¹ caused the virus to appear in the stools of monkeys inoculated parenterally. The virus may appear in the stools for two to four weeks before symptoms develop. In a series of papers published by Melnick's group¹⁰² it is shown that poliomyelitis virus, usually believed to disappear rather rapidly from the stools during convalescence, was still present in 13 per cent of 61 patients in the eighth week. In no case was the state of carrier prolonged as in cases of typhoid. Virus was detected for the first time in the blood of the patient. In another study the virus was isolated from the water of a creek near the residence of several patients.¹⁰³ That other modes of transmission are also of importance was illustrated in an explosive outbreak of poliomyelitis in a naval training school.¹⁰⁴ Eighteen attacks were diagnosed, and at least 100 milder ones developed within an eight day period. Evidence pointed to milk, possibly contaminated by flies, as the source of the infection.

These observations favor the view that poliomyelitis is transmitted chiefly in person to person contact by respiratory and oral transfer. Although murine strains of poliomyelitis virus were isolated from mice

101. Melnick, J. L.: The Recovery of Poliomyelitis Virus from the Stools of Monkeys and Chimpanzees Experimentally Infected by Various Routes, *Federation Proc.* **5**:250-251 (Feb.) 1946.

102. Horstmann, D. M.; Melnick, J. L., and Wenner, H. A.: Isolation of Poliomyelitis Virus from Human Extraneural Sources: Comparison of Virus Content of Pharyngeal Swabs, Oropharyngeal Washings and Stools of Patients, *J. Clin. Investigation* **25**:270-274 (March) 1946. Melnick, J. L.; Horstmann, D. M., and Ward, R.: Isolation of Poliomyelitis Virus from Human Extraneural Sources: Comparison of Virus Content of Blood, Oropharyngeal Washings and Stools of Contacts, *ibid.* **25**:275-277 (March) 1946. Horstmann, D. M.; Ward, R., and Melnick, J. L.: Isolation of Poliomyelitis Virus from Human Extraneural Sources: Persistence of Virus in Stools After Acute Infection, *ibid.* **25**:278-283 (March) 1946. Ward, R.; Horstmann, D. M., and Melnick, J. L.: Isolation of Poliomyelitis Virus from Human Extraneural Sources: Search for Virus in Blood of Patients, *ibid.* **25**:284-286 (March) 1946.

103. Toomey, J. A.; Takacs, W. S., and Weaver, H. M.: Isolation of Poliomyelitis Virus from Creek Water by Direct Transmission to Cotton Rat, *Am. J. Dis. Child.* **70**:293-297 (Nov.-Dec.) 1945.

104. Goldstein, D. M.; Hammon, W. M., and Viets, H. R.: An Outbreak of Polioencephalitis Among Navy Cadets, Possibly Food Borne, *J. A. M. A.* **131**:569-573 (June 15) 1946.

in New York, Jungeblut and Dalldorf¹⁰⁵ do not consider virus-harboring mice as a source of poliomyelitis in man.

Jungeblut's suggestion that a number of apparently similar viruses be included in a "poliomyelitis group" has not been generally adopted. There is reason to believe that several similar viruses may be included in a "poliomyelitis group." Further support for this view accrues in a study in which immunologic relations to other strains were found in one poliomyelitis virus which in its virulence for hamsters differed from the usual classic viruses, the Lansing strain and Theiler's mouse encephalomyelitis virus.¹⁰⁶

That tonsillectomy and the development of the bulbar form of poliomyelitis are related is reemphasized by studies of an epidemic in which it was found that 43 per cent of the children with this form of the disease had undergone tonsillectomy in the previous thirty days.¹⁰⁷ The incidence of poliomyelitis in children who had recently had their tonsils removed was 2.6 times that in other children, and that of the bulbar form was 16 times greater. According to Bodian,¹⁰⁸ lesions of the brain alone can produce the spasticity of acute poliomyelitis, and neither activity of the virus nor lesions of the spinal cord need be present. Nelson¹⁰⁹ suggests that a disturbance of the circulation and edema of the spinal cord are factors in the cause of the paralysis.

Aside from subjective improvement in a few of 34 patients with poliomyelitis, no encouraging results came from treatment with curare. According to Fox,¹¹⁰ curare is too dangerous a drug to be used in the acute phase of the disease. There is no evidence that gamma globulin or that serum in any form is of value in the treatment of the disease.¹¹¹

In a study to determine whether deficiency of other vitamins besides thiamine results in increased resistance of mice to poliomyelitis virus, it was observed that deficiency of pyridoxine, inositol and biotin caused

105. Jungeblut, C. W., and Dalldorf, G.: Epidemiological and Experimental Observations of Poliomyelitis in New York City (1943-1944), *Am. J. Hyg.* **46**:49-64 (Jan.) 1946.

106. Dalldorf, B., and Whitney, E.: Immunologic Relationships of MM, Lansing Poliomyelitis and Mouse Encephalomyelitis Virus, *Proc. Soc. Exper. Biol. & Med.* **59**:150-155 (June) 1945.

107. Anderson, J. A.: Poliomyelitis and Recent Tonsillectomy, *J. Pediat.* **27**: 68-70 (July) 1945.

108. Bodian, D.: Experimental Evidence on the Cerebral Origin of Muscle Spasticity in Acute Poliomyelitis, *Proc. Soc. Exper. Biol. & Med.* **61**:170-175 (Feb.) 1946.

109. Nelson, N.: Spinal Cord Circulation in Poliomyelitis, *Science* **104**: 49-50 (July 19) 1946.

110. Fox, M. J.: Curare in the Treatment of Acute Poliomyelitis, *J. A. M. A.* **131**:278-280 (May 25) 1946.

111. Bahlke, A. M., and Perkins, J. E.: Treatment of Preparalytic Poliomyelitis with Gamma Globulin, *J. A. M. A.* **129**:1146-1150 (Dec. 22) 1945.

no striking changes in the mice as compared with the controls.¹¹² Thiamine deficiency seems to be a specific factor in mice.

Mice treated with thiouracil are more susceptible to the virus of poliomyelitis than normal ones, but mice given thyroid substance are less so.¹¹³

St. Louis Encephalitis.—During interepidemic years 12 cases of St. Louis encephalitis, among 66 cases of acute encephalitis, were studied in a St. Louis hospital.¹¹⁴ Like the epidemic cases, all the sporadic cases occurred in the summer. It is obvious that the disease is endemic, probably maintained in a reservoir of blood-sucking ticks, mites or mosquitoes.

Viremia was demonstrated for the first time.¹¹⁵

Lymphocytic Choriomeningitis.—Mice may serve as a source of lymphocytic choriomeningitis. This disease occurred in 3 members of a household where infected mice were trapped.¹¹⁶ About 4 per cent of mice infesting houses in New York city carry the virus.

Japanese Encephalitis (Epidemic Encephalitis Type B).—Encephalitis caused by type B virus occurred in natives in the RyuKyu Islands in July 1945.¹¹⁷ One American soldier contracted the disease. This observation raises the question whether carriers have developed in troops of the United States and whether the infection will be brought to this country by returning veterans. At least seven species of mosquitoes in North America are capable of carrying the virus.¹¹⁸ Horses may be epidemiologic factors in Okinawa.¹¹⁹

112. Lichstein, H. C., and others: Influence of Pyridoxine, Inositol and Biotin on Susceptibility of Swiss Mice to Experimental Poliomyelitis, *Proc. Soc. Exper. Biol. & Med.* **60**:279-284 (Nov.) 1945.

113. Holtman, D. F.: The Effect of Thiouracil and Thyroactive Substances on Mouse Susceptibility to Poliomyelitis Virus, *Science* **104**:50-51 (July 19) 1946.

114. Blattner, R. J., and Heys, F. M.: St. Louis Encephalitis, *J. A. M. A.* **130**:854-857 (Nov. 24) 1945.

115. Blattner, R. J., and Heys, F. M.: Isolation of St. Louis Encephalitis from the Peripheral Blood of a Human Subject, *J. Pediat.* **28**:401-406 (April) 1946.

116. Dalldorf, G.; Jungeblut, C. W., and Umphlet, M. D.: Multiple Cases of Choriomeningitis in an Apartment Harboring Infected Mice, *J. A. M. A.* **131**:25 (May 4) 1946.

117. Hodes, H. L.; Thomas, L., and Peck, J. L.: Cause of an Outbreak of Encephalitis Established by Means of Complement-Fixation Tests, *Proc. Soc. Exper. Biol. & Med.* **60**:220-225 (Nov.) 1945.

118. Reeves, W. C., and Hammon, W. M.: Laboratory Transmissions of Japanese B Encephalitis Virus by Seven Species (Three Genera) of North American Mosquitoes, *J. Exper. Med.* **83**:185-194 (March) 1946.

119. Thomas, L., and Peck, J. L.: Results of Inoculating Okinawian Horses with the Virus of Japanese B Encephalitis, *Proc. Soc. Exper. Biol. & Med.* **61**:5-6 (Jan.) 1946.

Russian or Far Eastern tick-borne, spring-summer encephalitis is reviewed in a special supplement of the *American Review of Soviet Medicine*, 1946.

A hitherto undescribed form of viral encephalomyelitis was reported as occurring in water buffaloes of the western part of China.¹²⁰ The infection was transmitted to goats, guinea pigs and rabbits. It may have occurred in man through contact, but no case of this has as yet been recognized.

Smithburn and his associates¹²¹ report another "new" neurotropic virus isolated from mosquitoes in Africa, which they named Bunyamwera virus. Specific neutralizing antibodies were demonstrated in a number of persons in the area, which suggests that they had been infected previously.

Mumps.—Clinical and subclinical meningoencephalitis developed in 43 of 100 patients with mumps.¹²² Its occurrence was unrelated to the severity of salivary gland or orchitic involvement. A diagnosis can be made in the absence of the usual manifestations of the disease by specific serologic tests. Gamma globulin from mumps convalescent serum, but not that from pooled normal serums, seems to have some effect in the prevention of orchitis when given early in mumps.¹²³ Rambar's¹²⁴ studies show that orchitis developed in 16 per cent of patients who had received 40 cc. of mumps convalescent serum on admission and in 29 per cent of those who had not. Encephalitis occurred regardless of serum treatment. Serum given therapeutically had little or no effect in shortening the disease.

Rubella.—As Albaugh¹²⁵ points out, it is strange that no one before Gregg in 1942 was aware of the harmful effect which rubella (German measles) occurring in the mother during pregnancy has on the fetus, but a number of observers have since corroborated the observation. The critical period for the attack seems to be the first two months;

120. Sheng, T. S.: Virus Encephalitis in Buffaloes, *Science* **103**:344-346 (March 15) 1946.

121. Smithburn, K. C.; Haddow, A. J., and Mahoffy, A. F.: A Neurotropic Virus Isolated from *Aedes* Mosquitoes Caught in the Semliki Forest, *Am. J. Trop. Med.* **26**:189-208 (March) 1946.

122. Holden, E. M.; Eagles, A. Y., and Sturns, J. E.: Mumps Involvement of the Central Nervous System, *J. A. M. A.* **131**:382-385 (June 1) 1946.

123. Gellis, S. S.; McGuinness, A. C., and Peten, M.: A Study on the Prevention of Mumps Orchitis by Gamma Globulin, *Am. J. M. Sc.* **210**:661-664 (Nov.) 1945.

124. Rambar, A. C.: Mumps: Use of a Convalescent Serum in Treatment and Prophylaxis of Orchitis, *Am. J. Dis. Child.* **71**:1-13 (Jan.) 1946.

125. Albaugh, C. H.: Congenital Anomalies Following Maternal Rubella in Early Weeks of Pregnancy, *J. A. M. A.* **129**:719-723 (Nov. 10) 1945.

100 per cent of fetuses of mothers contracting rubella in this period are said to be injured. Of mothers contracting rubella in the third month, 50 per cent give birth to infants with congenital anomalies. The commonest defects are cataracts, cardiac septal defects, patent ductus arteriosus, deafness and microcephaly. Nearly all the infants are poorly developed. The observations indicate the need for enforcing strict preventive measures against rubella in pregnant women and for removing the stigma of hereditary transmission from defects of which rubella is the cause. One wonders whether other severe exanthems may give rise to similar defects in fetuses. Studies in Milwaukee do not bear out the high incidence of the condition. In a large outbreak of rubella¹²⁶ 9 women who were in an early stage of pregnancy contracted the disease. One bore a stillborn hydroencephalic infant; the offsprings of the rest were normal. One woman who did not have rubella bore an infant with congenital cataracts.

Infectious Hepatitis.—In a group of 572 campers infectious hepatitis affected 350 persons in a seven week period; ¹²⁷ 95 of these did not have jaundice. Infection was traced to a well that was probably polluted by cesspool drainage. Feces were thought to be the source of the infection because: in transmission experiments, water from the well caused mild attacks in 4 of 5 volunteers; volunteers inoculated with nasopharyngeal washings and with urine showed no effect; the causative filtrable agent was present in the blood and in the feces. In other experiments it was found that 1 part per million of chlorine added to the water was not enough to inactivate the virus.¹²⁸ It was necessary to maintain a concentration of 15 parts per million for thirty minutes. Treatment with sodium carbonate, aluminum sulfate and activated carbon did not completely inactivate the virus. In two other outbreaks circumstantial evidence suggested food as the source of the infection. In one outbreak milk was suspected,¹²⁹ and in the other¹³⁰ all victims of one epidemic ate meals together. In the latter there was a striking involvement of the lymphatic system resembling infectious mononucleosis, but there were no significant changes in the number or the kind of leukocytes in

126. Fox, M. J., and Bortin, M. M.: Rubella in Pregnancy Causing Malformation in the Newborn, *J. A. M. A.* **130**:568-569 (March 2) 1946.

127. Neefe, J. R., and Stokes, J.: An Epidemic of Infectious Hepatitis Apparently Due to a Water Borne Agent, *J. A. M. A.* **128**:1063-1075 (Aug. 11) 1945.

128. Neefe, J. R., and others: Disinfection of Water Containing Causative Agent of Infectious (Epidemic) Hepatitis, *J. A. M. A.* **128**:1076-1080 (Aug. 11) 1945.

129. Murphy, W. J., and Petrie, L. M.: Outbreak of Infectious Hepatitis, Apparently Milk-Borne, *Am. J. Pub. Health* **36**:169-173 (Feb.) 1946.

130. Read, M. R., and others: Infectious Hepatitis: Presumably Food-Borne Outbreak, *Am. J. Pub. Health* **36**:367-370 (April) 1946.

the blood. The epidemiologic features of infectious hepatitis are reviewed by Havens.¹³¹

The globulin of human immune serum (gamma globulin) is effective in preventing infectious hepatitis if injected intramuscularly during an outbreak.¹³² The passive immunity apparently lasts six to eight weeks. The globulin does not influence an attack if injected within six days before the onset or after the disease has begun.

Further experiments were made to learn whether infectious, or epidemic, hepatitis is identical with homologous serum jaundice. Havens¹³³ demonstrated in volunteers convalescent from serum jaundice a lack of immunity when they were inoculated with a strain of the virus of infectious hepatitis six months later, but this is in contrast with the previous report of Oliphant. The incubation period of infectious hepatitis was the same, twenty to thirty-four days if the inoculum was injected parenterally or fed. Havens' strain of infectious hepatitis virus inoculated parenterally or orally gives an incubation period of fifteen to thirty-four days, in contrast with fifty-six to one hundred and thirty-four days for the virus of homologous serum jaundice. The serum jaundice strain is not infectious if given orally, nor does it appear in the stools as the other virus does. Hepatitis virus injected parenterally does appear in the feces.¹³⁴ The inference is that the strains are different. Perhaps, as with other infectious agents, a group of similar and related viruses is operative. Others¹³⁵ were unable to transmit serum jaundice to volunteers by feeding stools from patients with serum jaundice but succeeded when stools from patients with infectious hepatitis were used. This may explain why epidemics of jaundice may arise from patients

131. Havens, W. P.: Epidemiological Studies on Infectious Hepatitis, *Am. J. Pub. Health* **36**:37-44 (Jan.) 1946.

132. Gellis, S. S., and others: The Use of Human Immune Serum Globulin (Gamma Globulin) in Infectious (Epidemic) Hepatitis in the Mediterranean Theater of Operation, *J. A. M. A.* **128**:1062-1063 (Aug. 11) 1945; The Use of Human Immune Serum Globulin (Gamma Globulin) in Infectious (Epidemic) Hepatitis in the Mediterranean Theater of Operation: II. Studies of Treatment in an Epidemic of Infectious Hepatitis, *ibid.* **128**:1158-1159 (Aug. 18) 1945. Havens, W. P., and Paul, J. R.: Prevention of Infectious Hepatitis with Gamma Globulin, *ibid.* **129**:270-272 (Sept. 22) 1945.

133. Havens, W. P.: Experiment in Cross Immunity Between Infectious Hepatitis and Homologous Serum Jaundice, *Proc. Soc. Exper. Biol. & Med.* **59**: 148-150 (June) 1945.

134. Havens, W. P., Jr.: Elimination in Human Feces of Infectious Hepatitis Virus Parenterally Introduced, *Proc. Soc. Exper. Biol. & Med.* **61**:210-212 (March) 1946; Viruses of Infectious Hepatitis and Serum Jaundice, *Federation Proc.* **5**:248 (Feb., pt. 2) 1946.

135. Neefe, J. R.; Stokes, J., and Reinhold, J. G.: Oral Administration to Volunteers of Feces from Patients with Homologous Serum Hepatitis and Infectious (Epidemic) Hepatitis, *Am. J. M. Sc.* **210**:29-32 (July) 1945.

with infectious hepatitis but not from those with serum jaundice. Three instances of hepatitis transmitted to recipients of transfusions of blood from donors who were in the incipient stage of the disease are reported. In Murphy's 2 patients¹³⁶ the period of incubation was twenty-four and forty-seven days, respectively, and in the patient studied by Francis' group,¹³⁷ eleven days. To reduce the danger that serum jaundice will be transmitted to persons who receive transfusions or injections of serum, Loutit and Maunsell¹³⁸ recommend that when possible the blood be taken from single sources rather than from pooled supplies. Freeman,¹³⁹ reverting to the problem of the jaundice that developed in persons vaccinated against yellow fever, suggests that the vaccine itself did not contain the infectious agent but had the property of predisposing its recipients to infectious hepatitis. He bases his views on the spatial and temporal grouping of attacks of jaundice in a military camp. It also seems possible in this instance, however, that an outbreak of post-vaccinal hepatitis coincided with an epidemic of infectious hepatitis.

Evidence of hepatitis or of an injury of the liver persists for many months in a certain proportion of the patients. In one group 18 per cent had prolonged lassitude, mental depression, abdominal discomfort, dyspepsia, subclinical jaundice and low fever.¹⁴⁰

In the series of patients studied by Hoagland and Shank,¹⁴¹ prompt hospitalization and rest were of greatest importance in treatment. No effect was noted from methionine, choline or liver extract or from diets high in protein or in carbohydrate when treated patients were compared with a control series. Recrudescences occurred in 18 per cent of patients. Observation has shown that the disappearance of jaundice does not always coincide with recovery.¹⁴² Exercise during active hepatitis causes a measurable increase in the size of the liver, tenderness and

136. Murphy, H. M.: Transmission of Infectious Hepatitis by Blood Transfusion: Report of Two Cases, *Gastroenterology* **5**:449-456 (Dec.) 1945.

137. Francis, T.; Frisch, A. W., and Quilligan, J. J.: Demonstration of Infectious Hepatitis Virus in Presymptomatic Period After Transfer by Transfusion, *Proc. Soc. Exper. Biol. & Med.* **61**:276-280 (March) 1946.

138. Loutit, J. F., and Maunsell, K.: Prevention of Homologous Serum Jaundice, *Brit. M. J.* **2**:759-760 (Dec. 1) 1945.

139. Freeman, G.: Epidemiology and Incubation Period of Jaundice Following Yellow Fever Vaccination, *Am. J. Trop. Med.* **26**:15-23 (Jan.) 1946.

140. Barker, M. H.; Capps, R. B., and Allen, F. W.: Chronic Hepatitis in the Mediterranean Theater: A New Clinical Syndrome, *J. A. M. A.* **129**:653-659 (Nov. 3) 1945.

141. Hoagland, C. L., and Shank, R. E.: Infectious Hepatitis: A Review of Two Hundred Cases, *J. A. M. A.* **130**:615-621 (March 9) 1946.

142. Capps, R. B., and Barker, M. H.: The Significance of Rest and Exercise in the Diagnosis and Management of Infectious Hepatitis, read at the meeting of the American Society of Clinical Investigation, 1946.

evidence of hepatic dysfunction, even without jaundice, an observation which emphasizes the importance of rest in treatment.

In 2 of 23 volunteers with infectious hepatitis, bacteremia with *Salmonella cholerae suis* developed. This occurrence suggests to Havens and Wenner¹⁴³ that infectious hepatitis may render the intestinal tract more susceptible to bacterial invasion. It may also explain the error made many years ago of ascribing the cause of infectious hepatitis to paratyphoid bacilli secondarily present in the blood. The name *S. cholerae suis*, or "hog cholera bacilli," represents an error of this sort. An example of a similar circumstance with a different disease probably occurred in an outbreak of infantile diarrhea.¹⁴⁴ A bacillus, tentatively called *B. mucosus capsulatus*, was recovered from the stools of most patients. It may have been a commensal.

Because jaundice at times relieves the symptoms of rheumatoid arthritis, 312 arthritic patients were inoculated with blood from patients with infectious hepatitis;¹⁴⁵ jaundice developed in only 32 of them. Ten were relieved of pain, and a few others were more comfortable, but the effect was short lived. This method of treatment is not recommended, because of the possible dangers of the induced disease.

Viral Myocarditis.—What appears to be a newly discovered filtrable virus able to cause myocarditis in animals was recovered from 2 monkeys by Helwig and Schmidt.¹⁴⁶ The virus was passed through many mice and regularly caused paralysis and myocarditis.

Although filtrable viruses are seldom regarded as the cause of myocardial disease occurring in man, the evidence that myocarditis due to such a virus occurs in monkeys, just described, is strongly suggestive that it may occur in man. That a specific myocardial disease accompanies mumps and influenza has been suspected for many years. Rosenberg¹⁴⁷ now reports evidence of myocardial involvement in 15 per cent of 104 cases of mumps. These reports, together with Finland's recent demonstration of myocarditis in a patient with influenza A, leave little doubt that viruses do cause myocarditis. Electrocardiographic changes

143. Havens, W. P., and Wenner, H. A.: Infectious Hepatitis Complicated by Secondary Invasion with *Salmonella*, *J. Clin. Investigation* **25**:45-52 (Jan.) 1946.

144. Walcher, D. N.: "Bacillus Mucosus Capsulatus" in Infantile Diarrhea, *J. Clin. Investigation* **25**:103-106 (Jan.) 1946.

145. Gardner, F.; Stewart, A., and MacCallum, F. O.: Therapeutic Effect of Induced Jaundice in Rheumatoid Arthritis, *Brit. M. J.* **2**:677-679 (Nov. 17) 1945.

146. Helwig, F. C., and Schmidt, E. C. H.: A Filter-Passing Agent Producing Interstitial Myocarditis in Anthropoid Apes and Small Animals, *Science* **102**: 31-33 (July 13) 1945.

147. Rosenberg, D. H.: Acute Myocarditis in Mumps (Epidemic Parotitis), *Arch. Int. Med.* **76**:257-267 (Nov.-Dec.) 1945.

in 4 cases of infectious mononucleosis suggested pericardial involvement.¹⁴⁸

DISEASES PROBABLY CAUSED BY VIRUSES.

Mononucleosis.—Fifteen patients with infectious mononucleosis gave evidence of hepatic disease but without jaundice.¹⁴⁹ Jaundice is well known to occur in patients with this disease and is usually ascribed to mechanical obstruction of the bile ducts by swollen lymph nodes. Evidence in mononucleosis now indicates the occurrence of active hepatitis akin to infectious hepatitis. Chronic hepatitis may follow.

Viral (?) Dysentery.—A fairly extensive outbreak of epidemic nausea, vomiting and diarrhea has again been reported from England, beginning in May 1945, similar to those which occurred in this country.¹⁵⁰ Other epidemics have been reported in personal letters.¹⁵¹ It is interesting to note how difficult it is to introduce a new term for a disease. The term "viral dysentery" was tentatively suggested¹⁵² to imply dysentery (bad bowel) probably caused by a virus, but three editorial comments¹⁵³ on the paper referred to are entitled "Gastric Influenza," "Virus Dysentery" and "Virus Enteritis," respectively.

In an outbreak of epidemic diarrhea of the newborn the gamma globulin given to 28 infants had no preventive or curative effect.¹⁵⁴

Pleurodynia.—Seventy-five patients with pleurodynia were studied in Alabama¹⁵⁵ between June and November 1944. Headache and paresthesias were often present in addition to the symptoms usually reported. It is hinted that a filtrable virus has been isolated from patients.

148. Evans, W. F., and Graybiel, A.: Electrocardiographic Evidence of Cardiac Complications in Infectious Mononucleosis, *Am. J. M. Sc.* **211**:220-226 (Feb.) 1946.

149. Cohn, C., and Lidman, B. J.: Hepatitis Without Jaundice in Infectious Mononucleosis, *J. Clin. Investigation* **25**:145-151 (Jan.) 1946.

150. Brown, G.; Crawford, G. J., and Stent, L.: Outbreak of Epidemic Diarrhea and Vomiting in a General Hospital and Surrounding District, *Brit. M. J.* **2**:524-527 (Oct. 20) 1945.

151. Epidemic Diarrhoea and Vomiting, Letters, *Brit. M. J.* **2**:666 (Nov. 10) 1945.

152. Reimann, H. A.; Price, A. H., and Hodges, J. H.: The Cause of Epidemic Diarrhea, Nausea and Vomiting (Viral Dysentery?), *Proc. Soc. Exper. Biol. & Med.* **59**:8-9 (May) 1945.

153. "Gastric Influenza," editorial, *Lancet* **2**:342 (Sept. 15) 1945. Virus Dysentery editorial, *J. A. M. A.* **129**:518-519 (Oct. 13) 1945. Virus Enteritis, editorial, *Lancet* **1**:62-63 (Jan. 12) 1946.

154. High, R. H., and others: Further Observations of Epidemic Diarrhea of the Newborn, *J. Pediat.* **28**:407-417 (April) 1946.

155. Nichamin, S. J.: Clinical and Epidemiologic Aspects of Epidemic Pleurodynia, *J. A. M. A.* **129**:600-605 (Oct. 27) 1945.

BACILLARY DISEASES

Bacillary Dysentery.—The confusion in the nomenclature of bacillary dysentery continues. A paper entitled "Shiga Dysentery"¹⁵⁶ describes experiences with the disease cause by *Shigella paradysenteriae*. In most readers' minds "Shiga dysentery" implies infection with the Shiga type of bacilli as distinguished from the Flexner type and other strains of "paradysentery" bacilli. Even the prefix "para" is unsatisfactory. Perhaps the term "shigellosis," as suggested by others, is preferable for the group of diseases to which the name of the causative agent of any of the component members can be added.

In the paper referred to it is stated that sulfadiazine given in the first twenty-four hours of disease gives the best results. Symptomatic relief, however, does not always indicate cure of the intestinal lesions, which may persist for several weeks, especially if treatment with sulfadiazine is started late. The use of the sigmoidoscope is as essential to diagnosis and management in dysentery as the otoscope is in diseases of the ear. Sulfadiazine is preferable to other sulfonamide compounds, according to Hardy.¹⁵⁷

In the experience of others,¹⁵⁸ in India, the clinical course of bacillary dysentery was not significantly affected by either sulfadiazine or sulfaguanidine. The alvine discharge and the duration of disease were the same in treated and in untreated patients. The lack of effect may be explained by the fact that treatment was often started too late, on the average five days after the onset; even so, many patients were treated on the first and second days. Another reason may be that the disease was mild; only 10 per cent were seriously sick, and none died. The authors also report that, contrary to general opinion, infection with *Shigella dysenteriae* was no more severe than infection with other members of the genus. Renal complications resulting from the use of sulfadiazine were common and often alarming.

Typhoid.—In an epidemic of typhoid 80 of 239 British soldiers who had had at least three yearly antityphoid vaccinations contracted the disease.¹⁵⁹ A few of them had received their last vaccination three weeks before the onset of the disease. The infection in those vaccinated was as severe as usual. The occurrence may cast grave doubt on the value of antityphoid vaccination, but vaccination, as the authors point out,

156. Smith, L. A.: Shiga Dysentery, J. A. M. A. **130**:18-22 (Jan. 5) 1946.

157. Hardy, A. V.: Studies of the Acute Diarrheal Diseases, Pub. Health Rep. **60**:1037-1042 (Sept. 7) 1945.

158. Elsom, K. A.; Pepper, D. S., and Forrester, J. S.: The Treatment of Bacillary Dysentery in Chinese Soldiers with Sulfaguanidine and Sulfadiazine, Am. J. M. Sc. **211**:103-109 (Jan.) 1946.

159. Jordan, J., and Everley, H.: Typhoid Fever in Immunized Personnel, Lancet **2**:333-335 (Sept. 15) 1945.

apparently prevented typhoid generally throughout the British Army, since no other similar outbreaks were reported. It is probable that the epidemic was caused by infection so massive as to break through the existent immunity. Similar experience was reported in studies on an outbreak in American troops in Guam.¹⁶⁰

In this country an outbreak of typhoid was traced to orange juice prepared by a carrier.¹⁶¹ Among 211 immunized persons who drank the juice only 1 contracted typhoid, while among 140 unvaccinated persons there were 17 attacks. Typhoid bacilli inoculated in orange juice remained viable at room temperature for six days.

Type specific bacteriophage was used with apparent success in the treatment of typhoid.^{161a} The results need confirmation.

The typing of typhoid bacilli is now on a firm basis and is of great value in epidemiology. Of 1,485 cultures obtained in Georgia, 1,153 could be classified by the bacteriophage method.¹⁶² Types A, E and C accounted for 72 per cent of them.

If a test proposed by Dennis and Saigh¹⁶³ is reliable, an important new diagnostic aid is at hand. According to the authors, the presence of an antigen of *Eberthella typhosa* can be demonstrated as early as the fifth day by the simple procedure of layering patient's serum on specific immune rabbit serum. A precipitate forms at the juncture. Absence of precipitate does not exclude typhoid.

Fowl is the greatest source of salmonella infection, or paratyphoid, and ducks and duck eggs are especially important. Evidence is now at hand implicating chicken eggs.¹⁶⁴ After an outbreak of "food poisoning" on a ship, *Salmonella Montevideo* was demonstrated as the internal contaminant of eggs.

Cholera.—In a paper¹⁶⁵ giving few technical details a naval unit reports amazing success in the treatment of cholera. All patients treated

160. Syverton, J. T., and others: Typhoid and Paratyphoid A in Immunized Military Personnel, *J. A. M. A.* **131**:507-514 (June 8) 1946.

161. Duncan, T. G., and others: Outbreak of Typhoid Fever with Orange Juice as the Vehicle, Illustrating the Value of Vaccination, *Am. J. Pub. Health* **36**:34-36 (Jan.) 1946.

161a. Knouf, E. G., and others: Treatment of Typhoid Fever with Type Specific Bacteriophage, *J. A. M. A.* **132**:134-137 (Sept. 21) 1946.

162. Morris, J. F.; Brin, A., and Sellers, T. F.: Types of *Eberthella Typhosa* Found in Georgia During the Four-Year Period 1941-1944, *J. Infect. Dis.* **77**: 25-27 (July-Aug.) 1945.

163. Dennis, E. W., and Saigh, A. S.: Precipitable Typhoid Bacterial Antigen in the Serum of Typhoid Fever Patients, *Science* **102**:280-282 (Sept. 14) 1945.

164. Watt, J.: An Outbreak of Salmonella Infection in Man from Infected Chicken Eggs, *Pub. Health Rep.* **60**:835-839 (July 20) 1945. Crowe, M.: Localized Outbreak of Salmonella Food Poisoning Apparently Transmitted by a Hen's Egg, *J. Hyg.* **44**:342-345 (May) 1946.

with plasma and sulfadiazine or sulfaguanidine recovered. Great stress is placed on the value of plasma injected intravenously despite a warning in United States Army Technical Bulletin 138 that plasma and whole blood generally are not necessary and "may be very harmful." The great difference in the mortality rates of 95 per cent in one control group and zero in a treated group seems exaggerated. In my own experience in Chungking, China, the mortality rate was 5 per cent in 160 patients treated energetically with isotonic solution of sodium chloride and sodium bicarbonate solution alone.¹⁶⁶ Because of many circumstances, including malnutrition, age, complications, other disease and late treatment, it seems reasonable to expect a mortality rate of at least 5 per cent in a disease as severe as cholera, no matter what treatment is given. No significant benefit was noted from the use of sulfonamide compounds, nor from streptomycin except for slight shortening of the attacks. According to a recent report, cholera has again broken out in Chungking, Shanghai and elsewhere in Asia.

The low mortality rate just described for well treated patients is in striking contrast to the rate for the epidemic which broke out in British prisoners of war in Siam.¹⁶⁷ Of 1,600 troops, 173 had cholera, and of these 100 died, or 58 per cent. Patients lived under harrowing conditions. No facilities for treatment were available. Even under such circumstances the mortality rate was not so high as stated, since mild attacks were admittedly not included statistically. Cholera was diagnosed only if patients were dehydrated and in a shocklike state. In the absence of laboratory aid, other rampant diarrheal diseases, especially bacillary dysentery, could not be differentiated from cholera.

In persons vaccinated against cholera agglutinins for brucella often develop, which may cause diagnostic confusion, especially in regard to veterans returning from the Asiatic area.¹⁶⁸ The reaction may be an anamnestic one or an H antigen may be common to both *Vibrio comma* and *Brucella*.

An epidemic first thought to be epidemic nausea, vomiting and diarrhea, occurring in Illinois, on investigation appeared to be caused by a

165. Report on Cholera Studies in Calcutta: Value of Chemotherapy in Treatment of Cholera and Use of Blood Plasma in Cholera Collapse, Epidemiology Unit no. 50, U. S. Nav. M. Bull. **45**:1049-1053 (Dec.) 1945.

166. Reimann, H. A., and others: Asiatic Cholera: Clinical Study and Experimental Therapy with Streptomycin, *Am. J. Trop. Med.* **26**:631-647 (Sept.) 1946.

167. DeWardener, H. E.: Cholera Epidemic Among Prisoners of War in Siam, *Lancet* **1**:637-640 (May 4) 1946.

168. Eisele, C. W., and others: Development of Brucella Agglutinins in Humans Following Vaccination for Cholera, *Proc. Soc. Exper. Biol. & Med.* **61**:89-91 (Jan.) 1946.

vibrio, *V. jejuni*, which causes enteritis in cows.¹⁶⁹ Presumably milk was the source of the vibrios. These were from the feces and the blood of some of the patients.

Brucellosis.—Chronic brucellosis is no doubt a medical problem but not so great as to be a potential danger to national health, according to a recent statement.¹⁷⁰ Space forbids combating many of the dubious statements made in this fanciful paper, which reveals a lack of knowledge of fundamental features of brucellosis; deserved criticism appears elsewhere.¹⁷¹ The endotoxin mentioned is hypothetic; the suggestion of performing cholecystectomy or splenectomy as therapy is unwarranted, and the criteria for diagnosis are insufficient. A positive cutaneous reaction alone cannot be relied on to establish the diagnosis. If the three complicated cases reported were selected as representative of cases of chronic brucellosis, one wonders how many of the 146 persons studied actually had the disease. According to Angle and his associates, brucellergin, on which the author depends so strongly, is not as reliable in cutaneous tests as heat-killed brucellas.¹⁷²

Tularemia.—In the epidemiologic study of tularemia rabbits should be distinguished from rodents. About 90 per cent of human attacks of tularemia result from contacts with rabbits, of which the cottontail is the most important in North America.¹⁷³ Other rabbits, hares, rodents, sheep, game birds, other animals, ticks and deer flies account for the rest.

Stuart and Pullen¹⁷⁴ review the literature on tularemic pneumonia and on tularemic meningitis and report cases of their own. An outbreak of tularemia due to tick-borne *Pasteurella tularensis* occurred among troops during maneuvers in Tennessee in 1943.¹⁷⁵ Larson¹⁷⁶ found the bacteria in the sputum of 3 patients with tularemia, 2 without evidence

169. Levy, A. J.: A Gastro-Enteritis Outbreak Probably Due to a Bovine Strain of *Vibrio*, *Yale J. Biol. & Med.* **18**:243-258 (March) 1946.

170. Benning, H. M.: Chronic Brucellosis: Success of Treatment with Brucellin, *J. A. M. A.* **130**:320-325 (Feb. 9) 1946.

171. Goodman, M. J.: Chronic Brucellosis, Correspondence, *J. A. M. A.* **131**: 30 (May 4) 1946.

172. Harris, H. J.: Diagnosis of Undulant Fever, Queries and Minor Notes, *J. A. M. A.* **130**:546 (Feb. 23) 1946.

173. Jellison, W. L., and Parker, R. R.: Rodents, Rabbits and Tularemia in North America: Some Zoological and Epidemiological Considerations, *Am. J. Trop. Med.* **25**:349-362 (July) 1945.

174. Stuart, B. M., and Pullen, R. L.: Tularemic Pneumonia: Review of American Literature and Report of Fifteen Additional Cases, *Am. J. M. Sc.* **210**: 223-236 (Aug.) 1945; Tularemic Meningitis: Review of Literature and Report of Case, with Postmortem Observations, *Arch. Int. Med.* **76**:163-166 (Sept.) 1945.

175. Warring, W. B., and Ruffin, J. S.: Tick-Borne Epidemic of Tularemia, *New England J. Med.* **234**:137-140 (Jan. 31) 1946.

176. Larson, C. L.: Isolation of *Pasteurella Tularensis* from Sputum, *Pub. Health Rep.* **60**:1049-1053 (Sept. 7) 1945.

of pulmonary involvement and the third with only roentgenographic evidence of it. It seems therefore that in making a diagnosis of tularemia the sputum should be inoculated into mice as a routine procedure.

Tetanus.—Boyd¹⁷⁷ reviews experience with tetanus as encountered during the war by physicians of the British Army. The incidence of the disease was negligible as compared with that in former wars. Reports of 103 cases were assembled. In only 22 cases was the patient a person who had been actively immunized, but the mortality rate in those who had been actively immunized did not fall below the usual level. The rate, however, was lower in those actively immunized who were given prophylactic antitoxin in addition; 100,000 units of antitoxin given intravenously within thirty-six hours after the first symptoms seemed to lower the mortality rate. Sedatives relieved symptoms but did not influence the course of the disease.

Pratt¹⁷⁸ reemphasizes the unsatisfactory state of the therapy of tetanus. In severe attacks treatment was ineffective, and most patients with mild attacks recovered. There was no evidence that 80,000 units of antitoxin was more effective than 30,000 units. Fatal reactions occurred when antitoxin was injected intrathecally in some patients who might otherwise have recovered; intrathecal therapy is not recommended. Excision of the site of infection, as expected, had no effect on the course of the disease.

Penicillin is of no value in the treatment of tetanus unless secondary invasion with bacteria sensitive to it takes place.¹⁷⁹

Diphtheria.—Delp and his associates¹⁸⁰ suggest that many patients now regarded as having the Guillain-Barré syndrome (virus encephalomyelitis) or infectious polyneuritis actually have diphtheritic paralysis. They report details of 5 cases. Their suggestion is important, for diphtheria has lost popularity, so to speak, and is not often in the modern physician's mind. Particularly confusing are cases of diphtheria of the skin.

Diphtheria is still a serious menace. It is among the chief causes of death in central Europe and in Japan.¹⁸¹ Its incidence is increasing in

177. Boyd, J. S. K.: Tetanus in the African and European Theater of War, 1939-1945, *Lancet* **1**:113-119 (Jan. 26) 1946.

178. Pratt, E. L.: Clinical Tetanus, *J. A. M. A.* **129**:1243-1247 (Dec. 29) 1945.

179. Altmeier, W. A.: Penicillin in Tetanus, *J. A. M. A.* **130**:67-72 (Jan. 12) 1946.

180. Delp, M. H.; Sutherland, G. F., and Hashinger, E. H.: Post-Diphtheritic Polyneuritis: A Report of Five Cases with Albuminocytologic Dissociation Simulating Guillain-Barré Syndrome, *Ann. Int. Med.* **24**:618-628 (April) 1946.

181. Diphtheria Still Leading Epidemic Disease, *Miscellaneous Topics*, *J. A. M. A.* **130**:89 (Jan. 12) 1946.

Germany and Finland. In Britain and Hungary, where immunization is possible, there are fewer cases.

Tuberculosis.—Biggs¹⁸² reemphasizes the subclinical nature of first attacks of tuberculosis. The diagnosis of a primary infection can be made only by a history of recent exposure and a tuberculin test. Serial roentgenograms aid in following its course. The author again raises the controversial question whether allergy is a beneficial or a harmful factor and plans to pursue the study further.

Dock¹⁸³ explains why tuberculosis so often attacks the upper lobes of the lungs: The erect position of man tends to reduce the amount of blood in the upper parts of the lungs. Perhaps this also accounts for the beneficial effects of prolonged rest in bed, since the flow of blood in the areas affected is increased by a recumbent position.

In spite of the fact that the Calmette-Guérin, or BCG, vaccine has been studied as a preventive of tuberculosis for more than twenty-five years, the reports of its value have been inconclusive. A recent study of 3,000 American Indians was made extending over a period of six years.¹⁸⁴ BCG vaccine was given to 1,550, and the rest served as controls. The results were encouraging; among the controls 48 died of tuberculosis in the six year period, compared with 9 of the vaccinated persons. BCG vaccine was used with great success in Denmark.^{184a} *Mycobacterium tuberculosis* from voles is a distinct strain but gives protection against other mammalian strains of tubercle bacilli when used as a vaccine. The vole strain vaccine was as effective as BCG vaccine in experimental studies.^{184b}

Dubos¹⁸⁵ reports a method by which *Mycobacterium tuberculosis* can be grown in seventy-two hours in Long's synthetic medium containing small amounts of phosphatides and esters of polyhydric alcohols. Other studies¹⁸⁶ show that certain water-soluble esters of fatty acids

182. Biggs, A. D.: A Roentgen Ray and Clinical Study of Primary Tuberculosis, *Arch. Int. Med.* **77**:393-404 (April) 1946.

183. Dock, W.: Apical Localization of Phthisis: The Significance in Treatment of Prolonged Rest in Bed, *Am. Rev. Tuberc.* **53**:297-306 (April) 1946.

184. Aronson, J. D., and Palmer, C. E.: Experience with BCG Vaccine in the Control of Tuberculosis Among North American Indians, *Pub. Health Rep.* **61**:802-820 (June 7) 1946.

184a. Holm, J.: Tuberculosis Control in Denmark, *Pub. Health Rep.* **61**:1426-1443 (Oct. 4); 1298-1315 (Sept. 6) 1946.

184b. Birkhaug, O. K.: Immunization with the Vole Bacillus, *Am. Rev. Tuberc.* **53**:411-418 (May) 1946.

185. Dubos, R.: Rapid and Submerged Growth of *Mycobacteria* in Liquid Media, *Proc. Soc. Exper. Biol. & Med.* **58**:361-362 (April) 1945.

186. Dubos, R., and Davis, B. D.: Factors Affecting the Growth of Tubercle Bacilli in Liquid Media, *J. Exper. Med.* **83**:409-423 (May) 1946.

increased the amount of growth. Serum albumin added to synthetic liquid mediums causes abundant growth in eleven to fifteen days.

Hamsters, once said to be suitable for routine diagnostic tests for tuberculosis, have been found highly resistant to a virulent strain of a human type of tubercle bacilli which caused widespread tuberculosis of guinea pigs.¹⁸⁷

Leprosy.—Many attempts have already been made to improve the unsatisfactory clinical classification of leprosy. Arnold and Tilden¹⁸⁸ propose one which seems to reconcile different points of view. They suggest the term "lepromatous leprosy" to include types which are generally strongly positive bacteriologically, have a bad prognosis, are relatively communicable, have a negative cutaneous reaction to lepromin and histologically show granulomatous tissue with bacillus-laden histiocytes. The term "tuberculoid leprosy" describes those which are usually negative bacteriologically, have a good prognosis, are slightly if at all communicable, have a positive cutaneous reaction to lepromin and histologically show tubercle-like aggregations of epithelioid cells and lymphocytes.

Although its specificity for *Mycobacterium leprae* cannot be demonstrated, Promin is at present the drug of choice in the treatment of leprosy.¹⁸⁹ Significant improvement occurred in 137 patients treated by Faget and Pogge. Improvement is slow but is evident after six months or more of intravenous injections given in courses. Promizole (4,2'-diaminophenyl-5-thiazolsulfone) and Diasone (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) are also of value in therapy.¹⁹⁰

Bubonic Plague.—An epidemic of plague broke out in Dakar, French West Africa, involving more than 500 people.¹⁹¹ Other outbreaks occurred in Taranto, Italy, and in Corsica. The disease was apparently imported by infected rats that had gained access to ships. Thirteen cases with 10 deaths occurred in Taranto in May and June 1945. The outbreaks were controlled by extermination of rats, by treatment of vermin

187. Steenken, W., and Wagley, P. F.: Comparison of the Golden Hamster to the Guinea Pig Following Inoculation of Virulent Tubercle Bacilli, *Proc. Soc. Exper. Biol. & Med.* **60**:255-257 (Nov.) 1945.

188. Arnold, H. L., and Tilden, I. L.: The Classification and Nomenclature of Leprosy with Suggestions for a Simplification of Both, *Ann. Int. Med.* **23**:65-73 (July) 1945.

189. Faget, G. H., and Pogge, R. C.: The Therapeutic Effect of Promin in Leprosy, *Pub. Health Rep.* **60**:1165-1171 (Oct. 5) 1945.

190. Faget, G. H.: Pogge, R. C., and Johansen, F. A.: Promizole Treatment of Leprosy, *Pub. Health Rep.* **61**:957-960 (June 28) 1946; Present Status of Diazone in the Treatment of Leprosy, *ibid.* **61**:960-963 (June 28) 1946.

191. Rotman, C. M. H.: Bubonic Plague in Dakar, *J. Roy. Nav. M. Serv.* **31**:155-158 (July) 1945. Epidemic of Plague in Corsica, *Foreign Letters, J. A. M. A.* **130**:964 (May 6) 1946.

with DDT powder (2,2-bis-(parachlorophenyl)-1,1,1-trichloroethane) and by use of vaccine. The use of DDT powder to control fleas and of sodium fluoroacetate (1080) to kill rats successfully stopped an epidemic of plague in Peru.^{191a} A list of reported cases of plague and deaths therefrom in the United States from 1900 to 1944 is published.¹⁹²

Three fatal cases of melioidosis are reported among soldiers of the United States, 2 in Guam and 1 in Burma.¹⁹³ Penicillin was ineffective.

COCCAL DISEASES

Subacute Bacterial Endocarditis.—Loewe and his associates¹⁹⁴ report the recovery of a strain of streptococci now designated as *Streptococcus* s. b. e. in 39 per cent of 106 cultures from patients with subacute bacterial endocarditis. These streptococci formed a rather homogeneous group mostly of one serologic type. A similar strain has thus far not been found in the oropharynx. It is highly resistant to penicillin. Others¹⁹⁵ find that streptococci isolated from patients and called alpha, or green-producing, streptococci are serologically identical and frequently belong to Lancefield's group D, as do most enterococci.

Meningococcic Meningitis.—Penicillin and sulfonamide compounds control the acute purulent reactions in patients with meningococcic meningitis, but unfortunately do not always prevent the coincident or the subsequent development of fibroblasts and scar tissue.¹⁹⁶ Therefore, neurologic sequels, such as paralysis, deafness and aphasia, still occur in treated patients.

Rheumatic Fever.—As may have been expected, evidence accumulates to oppose massive salicylate medication, which once was recommended by Coburn. In addition to the fatalities reported last year, further serious toxic reactions occurred when 350 micrograms of

191a. Macchiavello, A.: Plague Control with DDT and "1080": Results Achieved in a Plague Epidemic at Tumbes, Peru, 1945, *Am. J. Pub. Health* **36**:842-854 (Aug.) 1946.

192. Hampton, B. C.: Plague Infection Reported in the United States During 1944, and Summary of Human Cases, 1900-1944, *Pub. Health Rep.* **60**:1361-1365 (Nov. 16) 1945.

193. Mirick, G. S., and others: Melioidosis on Guam, *J. A. M. A.* **130**:1063-1067 (April 20) 1946. Cox, C. D., and Arbogast, J. L.: Melioidosis, *Am. J. Clin. Path.* **15**:567-570 (Dec.) 1945.

194. Loewe, L., and others: *Streptococcus* s.b.e. in Subacute Bacterial Endocarditis, *J. A. M. A.* **130**:257 (Feb. 2) 1946.

195. Wheeler, S. M., and Foley, G. E.: Note in Serologic Classification of Streptococci Isolated from Subacute Bacterial Endocarditis, *Am. Heart J.* **30**:511-513 (Nov.) 1945.

196. Bailey, P.: Chronic Leptomeningeal Thickening Following Treatment of Meningitis with Sulfa Drugs, *Ann. Surg.* **122**:917-925 (Dec.) 1945.

salicylate per cubic centimeter of serum was attained.¹⁹⁷ There is also little advantage gained by giving the drug intravenously instead of by the oral route. According to Murphy,¹⁹⁸ characteristic lesions of rheumatic pneumonia, tendon sheath nodules, tenosynovitis and an episcleral nodule developed while the amounts of salicylate in the serum rested between 300 and 600 micrograms. In one patient rheumatic activity developed in a joint for the first time during salicylate therapy. Since the drug has long been known to have no influence on the proliferative reaction of the disease or on its course and duration, serving only to relieve the symptoms, there is no point of giving more than just enough to produce comfort. Manchester^{197b} records 25 mg. of salicylate per 100 cc. of serum as satisfactory to suppress rheumatic activity. The amount is usually attained by giving from 10 to 12 Gm. of acetylsalicylic acid or of sodium salicylate together with 8 Gm. of sodium bicarbonate orally. Patients with heart failure are given aminopyrine daily until compensated, then sodium salicylate. He recommends intravenous medication in severe attacks or in those refractory to oral medication.

Guerra¹⁹⁹ gives the following theory to account for the clinical effect of salicylate relieving the symptoms of rheumatic fever. Strains of hemolytic streptococci are known to produce or possess hyaluronidase. The substance increases the spread of dyes when injected into tissue by decreasing viscosity which favors the passage of exudates and pathogenic bacteria. When sodium salicylate is given, it greatly inhibits the spreading effect of hyaluronidase and may thereby cause its beneficial effect in rheumatic fever.

If a new drug, succinyl acid benzyl ester, gives the beneficial effects described in recent report, it may supplant other "antirheumatic" agents.²⁰⁰ The results have not been confirmed.

According to two groups of investigators,²⁰¹ the electrocardiographic changes which follow postscarlatinal arthritis and carditis are the same

197. (a) Wegria, R., and Smull, K.: Salicylate Therapy in Acute Rheumatic Fever, *J. A. M. A.* **129**:485-490 (Oct. 13) 1945. (b) Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel, *ibid.* **131**:209-213 (May 18) 1946.

198. Murphy, G. E.: Salicylate and Rheumatic Activity: Objective Clinical Histological Study of Effect of Salicylate on Rheumatic Lesions, Those of the Joints and Tendon Sheaths in Particular, *Bull. Johns Hopkins Hosp.* **77**:1-42 (July) 1945.

199. Guerra, F.: Hyaluronidase Inhibition by Sodium Salicylate in Rheumatic Fever, *Science* **103**:686-687 (June 7) 1946.

200. Gubner, R., and Szucs, M.: Therapeutic Measures for Rheumatic Fever, *New England J. Med.* **233**:652-656 (Nov. 29) 1945.

201. Watson, R. F.; Rothbard, S., and Swift, H. F.: The Relationship of Postscarlatinal Arthritis and Carditis to Rheumatic Fever, *J. A. M. A.* **128**:

as those noted in cases of rheumatic fever. This suggests that in both instances they are streptococcic in origin. There are also no differences in the serum protein pattern revealed by electrophoresis as between rheumatic fever and scarlet fever. Steinmann,²⁰² a Swiss, believes that scarlatinal and rheumatic carditis are different.

Rantz and his co-workers²⁰³ believe that rheumatic fever is always a sequel to infection with hemolytic streptococci and that a continuing, potentially serious nonarthritic disease may occur as well. The presence or the absence of tonsils is of variable importance in different epidemics of streptococcic infection.

In a food-borne epidemic caused by type 1 hemolytic streptococci, nearly all the persons who became carriers of these cocci were sick. Most of them had follicular tonsillitis, but many mild attacks occurred which would not have been recognized as streptococcic infection if special laboratory studies had not been made. Patients who had had a previous attack of streptococcic infection seldom reacted with more than minimal clinical signs to reinfection with a new strain. It is possible that this type of mild infection may precede rheumatic fever and account for instances heretofore reported in which previous infection with hemolytic streptococci was supposedly absent or in which rheumatic fever seemed to be preceded by various nonstreptococcic conditions. The nature and the degree of pharyngeal tissue reaction to infection with hemolytic streptococci are highly variable and not necessarily related to the severity of the clinical response. It is obvious also that the eventual control of rheumatic fever will depend on the prevention and the control of infection with hemolytic streptococci.

Patients convalescing from rheumatic fever probably do not need so long a period of convalescence as is usually believed to be necessary. In one study²⁰⁴ patients convalescent from acute rheumatic fever were given graded exercises as soon as their clinical condition permitted. The usual laboratory criteria of recovery were not depended on. In another study,²⁰⁵ made at Randolph Field, Texas, patients could safely

1145-1152 (Aug. 18) 1945. Dole, V. P.; Watson, R. F., and Rothbard, S.: The Electrophoretic Changes in the Serum Protein Patterns of Patients with Scarlet Fever and Rh Fever, *J. Clin. Investigation* **24**:648-656 (Sept.) 1945. Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: Hemolytic Streptococcus Sore Throat, *Arch. Int. Med.* **76**:278-283 (Nov.-Dec.) 1945; Abnormalities in the Electrocardiogram Following Hemolytic Streptococcus Sore Throat, *ibid.* **77**:66-79 (Jan.) 1946.

202. Steinmann, B.: *Das Herz beim Scharlach*, Berne, Hans Huber, 1945.

203. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: The Etiology and Pathogenesis of Rheumatic Fever, *Arch. Int. Med.* **76**:131-137 (Sept.) 1945.

204. Robertson, H. F.; Schmidt, R. E., and Feiring, W.: Therapeutic Value of Early Physical Activity in Rheumatic Fever, *Am. J. M. Sc.* **211**:67-75 (Jan.) 1946.

205. Karpovich, P. V., and others: Physical Reconditioning After Rheumatic Fever, *J. A. M. A.* **130**:1198-1203 (April 27) 1946.

participate in graded exercises two weeks after the cessation of rheumatic activity. In both studies it was observed that the exercises improved the mental outlook of the patient, and caused no harmful effects.

Although rheumatic fever is said to be rare in tropical climates, the disease is not uncommon in Panama.²⁰⁶ Because numerous attacks have recently been recognized and older clinicians emphasized the danger of such a happening, it is suggested that the incidence of rheumatic fever has increased in Panama since 1927. No reason therefor is evident. Rheumatic heart disease is present also among the natives of New Guinea²⁰⁷ and among those of Curaçao,²⁰⁸

A puzzling precipitation which occurs when serum taken from a patient early in an attack of rheumatic fever is mixed with serum taken during the acute phase or during convalescence was thought to be a specific reaction.²⁰⁹ Further tests, however, showed that the reaction occurs, though less frequently, in other diseases as well. Whether the precipitate results from nonspecific changes in the albumin-globulin ratio or from formation of an auto-antigen-antibody system is unknown.

In a paper entitled "Direct Culture of Rheumatic Virus," the authors²¹⁰ caution readers not to be misled by the title. It seems that the blood of a patient with rheumatic fever contained something which produced peculiar transmissible changes in inoculated eggs, namely, thickening of the chorioallantois and redness of the embryo.

RICKETTSIAL DISEASES

There is a close relationship between the distribution of the Nuttall species of cottontail rabbits and the distribution of Rocky Mountain spotted fever in the western part of the United States.²¹¹ That species may be the important reservoir of infection in this region. Other

206. Hardgrove, M.; Whittier, L., and Smith, E. R.: Rheumatic Fever on the Isthmus of Panama, *J. A. M. A.* **130**:488-490 (Feb. 23) 1946.

207. Levine, H. D.: Rheumatic Heart Disease in New Guinea, Including a Cardiovascular Survey of Two Hundred Native Papuans, *Ann. Int. Med.* **24**:827-836 (May) 1946.

208. Hartz, P. H., and Van der Sar, A.: Occurrence of Rheumatic Carditis in the Native Population of Curaçao, Netherlands West Indies, *Arch. Path.* **41**: 32-38 (Jan.) 1946.

209. Wedum, A. G., and Wedum, B. G.: Serum Precipitation Reaction in Rheumatic Fever and in Other Conditions, *Proc. Soc. Exper. Biol. & Med.* **61**: 432-438 (April) 1946.

210. MacNeal, W. J., and others: Direct Culture of Rheumatic Virus, *Science* **103**:620-621 (May 17) 1946.

211. Jellison, W. L.: The Geographical Distribution of Rocky Mountain Spotted Fever and Nuttall's Cottontail in the Western United States, *Pub. Health Rep.* **60**:958-961 (Aug. 17) 1945.

species of cottontails are present in all areas where the disease has been recognized. Para-aminobenzoic acid was effective in the treatment of the disease experimentally established in guinea pigs,²¹² but penicillin was of no value.²¹³ In a survey in Texas 3.5 per cent of 4,219 persons had complement-fixing antibodies for murine typhus, suggesting that many more cases of typhus occur than are recognized.²¹⁴

Tsutsugamushi Disease.—The whole May 1945 issue of the *American Journal of Hygiene* is devoted to tsutsugamushi disease, giving a summary of the studies made in the New Guinea area. The disease, also known as scrub typhus, is widespread over an enormous area. The mites *Trombicula fletcheri* and *Trombicula walchi*, like *Trombicula akamushi*, which live on rodents, also carry *Rickettsia orientalis*, the causative agent. In experimental studies both immune rabbit serum²¹⁵ and para-aminobenzoic acid²¹⁶ were effective therapeutically. Tsutsugamushi disease has been recognized in the Philippine Islands for the first time.²¹⁷ The mortality rate among 240 patients was 4.5 per cent.

Para-aminobenzoic acid is effective for three rickettsial diseases: typhus,^{217a} Rocky Mountain spotted fever and tsutsugamushi. According to Greiff's theory,²¹⁸ the therapeutic effect is due to the drug's stimula-

212. Anigstein, L., and Bader, M. N.: Para-Aminobenzoic Acid: Its Effectiveness in Spotted Fever in Guinea Pigs, *Science* **101**:591-592 (June 8) 1945.

213. Fitzpatrick, F. K.: Penicillin in Experimental Spotted Fever, *Science* **102**:96-97 (July 27) 1945.

214. Davis, D. E., and Pollard, M.: Prevalence of Typhus Complement-Fixing Antibodies in Human Serums in San Antonio, Texas, *Pub. Health Rep.* **61**:928-931 (June 21) 1946.

215. Topping, N. H.: Tsutsugamushi Disease (Scrub Typhus): The Effects of an Immune Rabbit Serum in Experimentally Infected Mice, *Pub. Health Rep.* **60**:1215-1220 (Oct. 12) 1945.

216. Murray, E. S.; Zarafonetis, C. J. C., and Snyder, J. C.: Further Report on Effect of Para-Aminobenzoic Acid in Experimental Tsutsugamushi Disease, *Proc. Soc. Exper. Biol. & Med.* **60**:80-84 (Oct.) 1945. Snyder, J. C., and Zarafonetis, C. J. D.: Effects of Para-Aminobenzoic Acid in Experimental Tsutsugamushi Disease, *ibid.* **60**:115-117 (Oct.) 1945. Tierney, N. A.: Effect of Para-Aminobenzoic Acid in Tsutsugamushi Disease, *J. A. M. A.* **131**:280-285 (May 25) 1946.

217. Philip, C. B.; Woodward, T. E., and Sullivan, R. R.: Tsutsugamushi Disease (Scrub or Mite-Borne Typhus) in the Philippine Islands During American Re-Occupation in 1944-45, *Am. J. Trop. Med.* **26**:229-242 (March) 1946.

217a. Smith, P. K.: The Use of Para-Aminobenzoic Acid in Endemic (Murine) Typhus, *J. A. M. A.* **131**:1114-1117 (Aug. 3) 1946.

218. Greiff, D.; Pinkerton, H., and Moragues, V.: Defect of Enzyme Inhibitors and Activators on the Multiplication of Typhus *Rickettsia*: I. Penicillin, Para-Aminobenzoic Acid, Sodium Fluoride and Vitamins of the B Group, *J. Exper. Med.* **80**:561-574 (Dec.) 1944.

tion of the host cells' metabolism which probably interferes with the intracellular multiplication of the rickettsias.

Q Fever.—Several explosive outbreaks of pneumonia occurred among British and American troops in Greece and Italy.²¹⁹ In one unit 36 per cent of the personnel were sick. Each outbreak was related in some way to the living quarters or other locality of those who were sick. There was no evidence of person to person infection, and the period of incubation was about two weeks. A rickettsia was isolated, and serologic studies suggested that it was related to Q fever. An epidemic occurred in March 1946 in Texas,²²⁰ affecting 40 employees of a stockyard and meat packing plant. Variations in degree of severity were noted from mild influenza-like disease to severe pneumonia. Two patients died. Cattle were suspected to be the source of the infection.

Another outbreak of Q fever, affecting 26 persons, occurred in a laboratory.²²¹ The infection was thought to have been air borne. Persons who actually worked with the disease did not contract it. Apparently they had acquired immunity. The July 1946 issue of the *American Journal of Hygiene* contains twelve papers on the subject.

Pollard and others²²² report experiments which support their previous observations that Bullis fever is caused by a transmissible agent which can be cultured in the chick embryo. The agent originated from ticks near Camp Bullis in Texas. Minute coccobacillary bodies were found in lymphoid cells, unlike those described in Colorado tick fever, from which Bullis fever is different immunologically as well. They also found Colorado tick fever to differ immunologically from dengue. Despite many similarities the two are probably different diseases. A denguelike fever has been observed for the first time in Puerto Rico.²²³

Further studies on Colorado tick fever show that it is caused by a virus which passes through membranes of 24 millimicron porosity.²²⁴

219. Outbreaks of a Rickettsial Disease Related to Q Fever, Bull. U. S. Army M. Dept. 5:245-246 (March) 1946.

220. Irons, J. V., and others: Outbreak of Q Fever, in the United States, Pub. Health Rep. 61:784-785 (May 31) 1946.

221. Outbreak of Q Fever Among Bethesda Research Workers, Washington Letter, J. A. M. A. 130:720 (March 16) 1946.

222. Pollard, M.; Livesay, H. R.; Wilson, D. J., and Woodland, J. C.: Experimental Studies with Bullis Fever, Am. J. Trop. Med. 26:175-187 (March) 1946; Immunological Studies of Dengue Fever and Colorado Tick Fever, Proc. Soc. Exper. Biol. & Med. 61:396-398 (April) 1946.

223. Diaz-Rivera, R. S.: A Bizarre Type of Seven Day Fever Clinically Indistinguishable from Dengue, Bol. Asoc. méd. Puerto Rico 38:75-80 (March) 1946.

224. Florio, L.; Stewart, M. O., and Mugrage, E. R.: The Etiology of Colorado Tick Fever, J. Exper. Med. 83:1-10 (Jan.) 1946.

SPIROCHETAL DISEASES

Relapsing Fever.—Eleven cases of relapsing fever caused by *Spirochaeta recurrentis* were observed in Texas.²²⁵ In several instances this sickness was confused with other diseases but the diagnosis was established when the spirochete was observed in the blood during the febrile episode and, in 1 instance in sections of a cutaneous lesion during the afebrile period. Oxophenarsine hydrochloride did not prevent relapses and gave disappointing results in 7 patients. Penicillin was said to be more effective in 2 patients. Experience²²⁶ with relapsing fever, probably caused by *S. recurrentis*, in India indicates that better results are obtained with arsenical therapy. Oxophenarsine hydrochloride was used.

Penicillin was as effective as neoarsphenamine in an outbreak in Tunisia²²⁷ but the latter is cheaper and easier to give. Penicillin is preferable if jaundice is present.

Rat Bite Fever.—Penicillin is reported to have been of value in rat bite fever caused by *Streptobacillus moniliformis*; 5 cases were studied.²²⁸ In a case caused by *Spirillum minus*, the spirillum was demonstrated in the lymph of the primary wound for the first time. Swyer²²⁹ reports a case of rat bite fever caused by the bite of a cat. Penicillin was said to have been curative.

Spirochetal Jaundice.—Jaundice due to *Leptospira icterohaemorrhagiae*, or Weil's disease, affected at least 17 British soldiers who had bathed in the River Arno or in the water of bomb craters.²³⁰ Five died. Patients treated with penicillin or with antileptospiral serum did not show any beneficial effect as compared with untreated patients. Although many attacks of infectious hepatitis occurred at the same time there, the authors said they had practically no difficulty in diagnosis of either disease, but one wonders how mild cases of leptospirosis, particularly nonicteric ones, can be so easily differentiated. Evidence of

225. Taft, W. C., and Pike, J. B.: Relapsing Fever: Report of a Sporadic Outbreak, Including Treatment with Penicillin, J. A. M. A. **129**:102-104 (Dec. 8) 1945.

226. Wolff, B. P.: Asiatic Relapsing Fever: Report of One Hundred and Thirty-Four Cases Treated with Mapharsen, Ann. Int. Med. **24**:203-216 (Feb.) 1946.

227. Greaves, F. G.; Gezon, H. M., and Alston, W. F.: Louse-Borne Relapsing Fever in Tunisia, U. S. Nav. M. Bull. **45**:1029-1048 (Dec.) 1945.

228. Watkins, C. G.: Ratbite Fever, J. Pediat. **28**:429-448 (April) 1946.

229. Swyer, G. I. M.: Rat Bite Fever Due to Cat Bite: Satisfactory Response to Penicillin After Failure of Arsenotherapy, Brit. M. J. **2**:386-388 (Sept. 22) 1945.

230. Hutchinson, J. H., and others: Outbreak of Weil's Disease in the British Army in Italy, Brit. M. J. **1**:81-83 (Jan. 19) 1946.

nephritis without jaundice may be the predominant manifestation of the disease.^{230a}

Contrary to previous reports, not all strains of white mice are susceptible to infection with *L. icterohaemorrhagiae* when inoculated for diagnosis.²³¹

Swine and cattle are now incriminated as carriers of leptospiras, and they transmit the organisms to man. Gsell in Switzerland²³² studied swineherd's disease, which is characterized by serous meningitis and formerly was thought to be viral in origin. He found agglutinin for *Leptospira pomona* in high titer. Sixty-five per cent of hogs tested also had the agglutinin in high titer, and *L. pomona* was in the urine of 2. He quotes Clayton, of Australia, as having demonstrated *L. pomona* in dairy workers. Probably a similar or an identical agent was recognized in Russia and in Palestine, where Bernkopf²³³ called it *Leptospira bovis*.

PROTOZOAL DISEASES

Malaria.—*Plasmodium vivax* malaria caused the Kahn flocculation test for syphilis to show a positive reaction in 33 and a doubtful reaction in 11 of 100 cases of malaria.²³⁴ The test became negative in 84 per cent in four weeks, and negative in all cases at eleven weeks. No change occurred in the spinal fluid.

Reports²³⁵ have appeared concerning the toxic effects of quinacrine hydrochloride (atabrine): an "atabrine dermatitis complex," aplastic anemia, neutropenia, hepatitis and toxic psychosis. The mortality rate has been high. In spite of these rare occurrences, the value of the drug outweighs the untoward effects attributed to it.

Attempts have been made to provide a better drug. A new compound called M. 4888, or paludrine, (N_1 -p-chlorophenyl- N_5 isopropyl biguanide) is reported from England.²³⁶ In daily doses of 10 to 15 mg.

230a. Stiles, W. W.; Goldstein, J. D., and McCann, W. S.: Leptospiral Nephritis, *J. A. M. A.* **131**:1271-1274 (Aug. 17) 1946.

231. Stavitsky, A. B., and Green, R. G.: Susceptibility of the Young White Mouse (*Mus Musculus*) to Experimental Leptospirosis, *Science* **102**:352-353 (Oct. 5) 1945.

232. Gsell, O.: Disease of Swineherds Caused by *Leptospira Pomona*, *Presse méd.* **53**:525-526 (Sept. 29) 1945.

233. Infection with Bovine Leptospirosis in Man in Palestine, *Foreign Letters*, *J. A. M. A.* **131**:250 (May 18) 1946.

234. Robinson, H. M., and McKinney, W. W.: The Effect of Vivax Malaria on Spinal Fluid and Blood Serologic Tests for Syphilis, *J. A. M. A.* **129**:667-668 (Nov. 3) 1945.

235. Untoward Reactions Attributable to Atabrine, Special Article, *J. A. M. A.* **129**:1091-1093 (Dec. 15) 1945.

236. Triumph Against Malaria, *Brit. M. J.* **2**:653-654 (Nov. 10) 1945.

it effectively terminates benign tertian malaria but does not prevent relapse. In daily doses of 0.1 Gm. it effectively prevents clinical signs of malaria but does not prevent infection. It is said to be superior to both quinine and quinacrine hydrochloride and, unlike the latter, does not stain the skin yellow. Not enough trial has been made to learn what possible toxic effect may follow its use.

Similar statements may be made about chloroquine, studied by Americans.²³⁷ This drug is also said to be an effective suppressive. It is said to cause abrupt ending of a clinical attack of *P. vivax* malaria and to cure *Plasmodium falciparum* malaria in one or two days. It does not discolor the skin. Pentaquine (SN 13,276) is too toxic as a suppressive agent but, together with quinine, cures severe infection due to *P. vivax*.^{237a} According to recent unpublished information, a reevaluation shows plasmochin and related compounds to be the most effective agents used to prevent relapses in malaria, although toxic effects are relatively common.

Further study following Coggeshall's demonstration of an immune reaction of monkeys to malaria shows that these animals can be partially protected against *Plasmodium knowlesi* infection with a vaccine composed of killed parasites together with oily substances and killed tubercle bacilli.²³⁸

Most and Hayman²³⁹ point out the bizarre clinical forms in which *P. vivax* malaria may occur. Especially puzzling from the point of view of diagnosis will be malaria in returned service men in whom the disease was suppressed so long as quinacrine hydrochloride was taken. The disease may first appear a year afterward and assume diverse clinical forms. It may cause signs and symptoms resembling appendicitis and cholecystitis; there may be nausea, vomiting and diarrhea; urticaria may develop; pneumonia may be suspected. It must also be remembered that patients who have had malaria may actually have appendicitis, cholecystitis, tonsillitis, pneumonia and other diseases.

237. Wartime Research in Malaria, Board for the Coordination of Malarial Studies, Science **103**:8-9 (Jan. 4) 1946. Loeb, R. F., and others: Activity of Antimalarial Agent Chloroquine (SN 7618), J. A. M. A. **130**:1069-1070 (April 20) 1946. Most, H., and others: Chloroquinone for Treatment of Vivax Malaria, *ibid.* **131**:963-967 (July 20) 1946.

237a. Loeb, R. F.: Activity of a New Antimalarial Agent, Pentaquine (SN 13,276), J. A. M. A. **132**:321-323 (Oct. 12) 1946.

238. Freund, J., and others: Immunization of Rhesus Monkeys Against Malarial Infection (*P. Knowlesi*) with Killed Parasites and Adjuvants, Science **102**:202-204 (Aug. 24) 1945.

239. Most, H., and Hayman, J. M.: Uncommon Clinical Manifestations of Vivax Malaria, J. A. M. A. **130**:480-485 (Feb. 23) 1946.

Experiments on patients showed that anoxia as experienced at high altitudes did not cause relapse or parasitemia in persons recently recovered from malaria.²⁴⁰

Kala Azar.—Kala azar in military personnel who have served in endemic areas may give diagnostic difficulties if it develops after their return home. Months may elapse after infection before symptoms begin. Two instances are reported in England in which soldiers who returned from the Mediterranean area with the infection had only slight fever, malaise, splenomegaly and leukopenia many months after their exposure in North Africa.²⁴¹ The title of the author's paper is misleading; his patients were not asymptomatic, but they did not reveal their symptoms until questioned.

Packchanian²⁴² reports 2 cases of kala azar occurring in American soldiers who had served in the Near East. The diagnosis can be made only after the organism has been cultivated from a lesion of the skin or from the blood, the bone marrow, the spleen or the liver and identified. Since the diagnosis cannot be made by examining stained smears alone, in which yeast or other extraneous material may be mistaken for Leishmania, both Packchanian and Wenyon question Benedek's diagnosis of the first supposed autochthonous case in the United States.

According to South American physicians, an autochthonous case of American visceral leishmaniasis was reported by Penna in 1934.²⁴³ Tavares reported the first diagnosis made during life and now reports a second. A new species, *Leishmania chagasi*, is described. No details are given as to how the diagnosis was proved or how closely *L. chagasi* is related to *Leishmania donovani* or *Leishmania tropica*.

Van Dyke and Gellhorn²⁴⁴ tested a large number of antimonial and other compounds to find a more effective therapeutic agent for leishmaniasis, but none was superior to diethylaminoethanol of sodium antimony gluconate (Stibanose), stibamine glucoside (Neostam) or ethylstibamine (Neostibosan), which are now in use.

Kala azar is characterized by hyperinosemia, yet amyloid disease has not been reported to be present during this infection. Amyloid disease often occurs in mice inoculated with *L. donovani*.²⁴⁵

240. Howe, C. D., and Duffe, F. L.: Effect of Altitude Anoxia in Provoking Relapse in Malaria, *Science* **103**:223 (Feb. 22) 1946.

241. Armstrong, T. G.: Asymptomatic Kala-Azar in Soldiers from Overseas, *Brit. M. J.* **2**:918 (Dec. 29) 1945.

242. Packchanian, A.: Leishmaniasis, *J. A. M. A.* **129**:544-547 (Oct. 20) 1945.

243. American Visceral Leishmaniasis, *Foreign Letters, J. A. M. A.* **129**:761-762 (Nov. 10) 1945.

244. Van Dyke, H. B., and Gellhorn, A.: Chemotherapy of Experimental Leishmaniasis, *Proc. Soc. Exper. Biol. & Med.* **61**:403-405 (April) 1946.

245. Gellhorn, A., and others: Amyloidosis in Hamsters with Leishmaniasis, *Proc. Soc. Exper. Biol. & Med.* **61**:25-30 (Jan.) 1946.

American Trypanosomiasis.—Two soldiers contracted American trypanosomiasis (Chagas' disease) in Panama and were seriously sick.²⁴⁶ Prominent articular symptoms resembled those of rheumatic fever. Lymphocytosis was present. Stibophen (Fuadin) seemed to have therapeutic value.

Coccidiosis.—Human coccidiosis (*Isospora hominis* infection) is rare but is thought to have caused the symptoms of diarrhea, abdominal pain and eosinophilia of 3 patients.²⁴⁷ *Isospora* was present in the stools. It is usually hard to be sure whether the organisms are pathogens or saprophytes.

METAZOAL DISEASES

The problem of the control of trichinosis is discussed by Gould,²⁴⁸ who calculates that the average American during his lifetime eats about two hundred meals of pork containing trichinas. Each of these would be harmless if the pork were properly cooked, but many chances of infection persist. Although most of the pork (70 per cent) available is processed under federal inspection, the larger part of the total supply is likely to be infected. The most important factor in the control of the disease is the eradication of the infected hogs. The incidence of trichinosis of hogs (1.5 per cent) has not been changed in fifty years. The incidence of infection in Germany was 0.001 per cent and that in Denmark much less.

Filariasis.—Coggeshall²⁴⁹ reviews the important features of filariasis as these pertain to military personnel stationed in areas in which the disease is endemic. Although about 38,000 men were exposed, the infection was diagnosed in only about 10,000. The disease was usually mild and characterized in its early stage by lymphopharyngitis, lymphedema, lymphadenitis and funiculitis, as well as by aches and pains in the major lymphatic areas. Elephantiasis or other disabling effects did not occur and probably will not, because the infection was light. The filarias cannot multiply in infected patients unless they undergo further passage in mosquitoes, and there is little chance that they will survive in this country. There are no reliable specific therapeutic agents.

After patients are removed from the areas in which the disease is endemic, the infection disappears, and they are usually symptom free.

246. Moseley, V., and Miller, H.: South American Trypanosomiasis (Chagas' Disease), *Arch. Int. Med.* **76**:219-229 (Oct.) 1945.

247. Humphrey, A. A.: *Isospora Hominis* Infection in Man, *J. A. M. A.* **130**:143-145 (Jan. 19) 1946.

248. Gould, S. E.: An Effective Method for the Control of Trichinosis in the United States, *J. A. M. A.* **129**:1251-1254 (Dec. 29) 1945.

249. Coggeshall, L. T.: Filariasis in the Serviceman: Retrospect and Prospect, *J. A. M. A.* **131**:8-12 (May 4) 1946.

Incapacitating sequels were observed in only 0.2 per cent of Zeligs' ²⁵⁰ patients and in 3 of the 532 patients of Behm and Hayman. ²⁵¹

The diagnosis was often made without the causative organisms being demonstrated. Laboratory tests other than that for eosinophilia are seldom helpful. Filarias are rarely found. ²⁵²

Moniliasis.—A patient with pulmonary moniliasis recovered promptly after being treated with small amounts of specific immune serum—which represents a new idea concerning the therapy of mycotic disease. ²⁵³ There is, however, little proof that the disease was moniliasis. The diagnosis was based on a reaction of the skin to an injection of immune rabbit serum and a culture of sputum which showed *Candida albicans*, but there is no mention of smears showing the presence of this organism. A skin test with the monilia elicited no significant reaction, and specific agglutinins did not develop until after the patient had been treated with the immune serum.

Reiter's Disease.—Reiter's disease, characterized by urethritis, conjunctivitis, arthritis and diarrhea, may be mistaken for gonorrhea. Twenty-five cases of a disease resembling Reiter's were reported by Hollander and co-workers ²⁵⁴ from an Army hospital for patients with arthritis. The literature on the subject was collected and reviewed by Vallee. ²⁵⁵ While the cause is unknown, studies by Dienes ²⁵⁶ point to organisms of the pleuropneumonia group. These were found in the prostatic secretion of 4 patients with the syndrome and in the synovial fluid of 1. The Stevens-Johnson syndrome is like Reiter's disease except for a cutaneous eruption and stomatitis. Two cases are reported by Kove. ²⁵⁷ An epidemic of epididymo-orchitis of unknown cause occurred among soldiers in Malta characterized by two phase fever and unilateral testicular swelling. ²⁵⁸ It was not caused by brucellosis or by sandfly fever.

250. Zeligs, M. A.: Psychosomatic Aspects of Filariasis, *J. A. M. A.* **128**: 1139-1142 (Aug. 18) 1945.

251. Behm, A. W., and Hayman, J. M.: The Course of Filariasis After Removal from an Endemic Area, *Am. J. M. Sc.* **211**:385-394 (April) 1946.

252. Hodge, I. G.; Denhoff, E., and Vanderveer, J. B.: Early Filariasis (Bancrofti) in American Soldiers, *Am. J. M. Sc.* **210**:207-222 (Aug.) 1945.

253. Hiatt, J. S., and Martin, D. S.: Recovery from Pulmonary Moniliasis Following Serum Therapy, *J. A. M. A.* **130**:205-206 (Jan. 26) 1946.

254. Hollander, J. L., and others: Arthritis Resembling Reiter's Syndrome: Observation on Twenty-Five Cases, *J. A. M. A.* **129**:593-595 (Oct. 27) 1945.

255. Vallee, B. L.: Reiter's Disease: Review of Literature, with Presentation of a Case, *Arch. Int. Med.* **77**:295-306 (March) 1946.

256. Dienes, L.; Smith, C., and Ropes, M. W.: Studies of the Incidence and Pathogenicity of Pleuropneumonia-like Organism in Humans, read at the meeting of the American Society of Clinical Investigation, May 27, 1946.

257. Kove, S.: Stevens-Johnson Syndrome (Eruptive Fever with Stomatitis and Conjunctivitis), *Am. J. M. Sc.* **210**:611-623 (Nov.) 1945.

MISCELLANEOUS

Origin of Viruses.—Two monographs have been published which are of importance to all who are interested in infections. One is by Dubos²⁵⁹; the other, by Burnet.²⁶⁰ Burnet subscribes to the view that viruses are living forms which have evolved, by parasitic degeneration, from larger micro-organisms, such as bacteria, fungi or protozoa. Unless viruses are in a biologic class by themselves, it would seem that this theory runs counter to general evolutionary procedure in which organisms seem to evolve by gaining various powers and increasing in complexity. There would seem to be as much logic in the opposite view that viruses, by mutation, are the source of higher forms of life, as follows—viruses→psittacosis group→rickettsias→bacteria→protozoa, fungi and others. Although it is now well known that certain bacteria have filtrable variant forms—for example, the pleuropneumonia organisms and *Bacillus tularensis* (Foshay)—there is no evidence that any of these variants should be regarded as true filtrable viruses.

Burnet also holds that all or nearly all the known virus diseases of man have been derived from animals. Psittacosis, St. Louis encephalitis, equine encephalitis and Q fever, he suggests, are “new” diseases, all having appeared in the last fifty years, but just because these diseases have been recognized recently by the development of new knowledge and technic does not mean that they have not been prevalent but unrecognized for centuries. Nevertheless, it is possible that genuinely new infections may arise from time to time by the appearance of mutant forms among known viruses or bacteria, which may find in man an environment suitable for their growth.

Bacterial Variation.—Although the phenomenon of bacterial variation has been studied for many years, it has seemed to be chiefly a matter of academic interest. There is no evidence that recovery from infectious disease depends primarily on a change from virulence to avirulence of bacteria, but there seems to be no doubt that the instability of most bacteria and their constant changing into various forms is of practical importance from the standpoint of epidemiology, etiology and diagnosis and in the preparation of vaccines.²⁶¹

There is also no doubt but that variation of form causing the colonies to differ from the usual ones may at times prevent their recognition

258. Tunbridge, R. E., and Gavey, C. J.: Epidemic Epididymo-Orchitis in Malta, *Lancet* 1:775-779 (May 25) 1946.

259. Dubos, R. J.: *The Bacterial Cell*, Harvard University Monograph in Medicine and Public Health no. 6, Cambridge, Mass., 1945.

260. Burnet, F. M.: *Virus as Organism*, Harvard University Monograph in Medicine and Public Health no. 8, Cambridge, Mass., 1945.

261. Reimann, H. A.: The Significance of Bacterial Type Transformation in Infectious Diseases and Epidemiology, *Tr. A. Am. Physicians* 53:270-273, 1938.

on diagnostic culture mediums. For example, "small colony forms" of typhoid bacilli isolated from patients with typhoid may not be recognized as such without further study because of their unusual smallness. Chronic carriers of *Vibrio comma* are thought not to exist, but perhaps carriers shed *V. comma* in a variant phase in which the organisms grow in unrecognizable colonies.

Morton and Shoemaker²⁶² now report the recovery of small colony variants of gonococci from 3 patients with gonorrhea. These colonies composed of gram-negative cocci were five to ten times smaller than the usual ones and would ordinarily not be suspected of being colonies of *Neisseria gonorrhoeae*. On serial culture, however, they reverted to the usual colony forms.

Diet and Resistance.—Important studies on the relation of diet to the power to resist infection were made by Schneider and Webster.²⁶³ In extensive experiments the natural resistance of mice to *Salmonella enteritidis* was best maintained by a diet of whole wheat and dried milk, in which the "natural" elements, or "immunogen," in whole wheat were the more important.

In other studies,²⁶⁴ rats and mice given a diet deficient in thiamine were more susceptible to oral infections with *Salmonella typhi murium* than those given an adequate diet. In mice the diminished resistance was specifically due to the deficiency of thiamine, but in rats the inanition which accompanies avitaminosis was responsible. The experiments provide further evidence that one cannot generalize in regard to the effect of avitaminosis on susceptibility to various infections, as previously shown in experiments with poliomyelitis. Different species of animals behave differently.

Pyridoxine deficiency impedes the development of antibodies.²⁶⁵ Antibody production depends on an adequate supply of essential amino acids,²⁶⁶ yet in certain experiments,²⁶⁵ animals fed restricted amounts of food developed antibody titers fivefold higher than animals given an unlimited diet.

262. Morton, H. E., and Shoemaker, J.: The Identification of *Neisseria Gonorrhoeae* by Means of Bacterial Variation and the Detection of Small Colony Forms in Clinical Material, *J. Bact.* **50**:585-587 (Nov.) 1945.

263. Schneider, H. A., and Webster, L. T.: Nutrition of the Host and Natural Resistance to Infection, *J. Exper. Med.* **81**:359-384 (April) 1945.

264. Guggenheim, K., and Beuchler, E.: Thiamin Deficiency of Rats and Mice to Infection with *Salmonella Typhi Murium*, *Proc. Soc. Exper. Biol. & Med.* **61**:413-416 (April) 1946.

265. Stoerck, H. C., and Eisen, H. N.: Suppression of Circulating Antibodies in Pyridoxine Deficiency, *Proc. Soc. Exper. Biol. & Med.* **62**:88-89 (May) 1946.

266. Wissler, R. W.; Woodridge, R. L., and Steffee, C. H.: Influence of Amino Acid Feeding upon Antibody Production, *Proc. Soc. Exper. Biol. & Med.* **62**:199-203 (June) 1946.

Book Reviews

Protozoology. By Richard R. Kudo, D.Sc. Third Edition. Price, \$8. Pp. 778, with 336 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1944.

Although written by a zoologist and not primarily for physicians, this book seems admirably suited for the physician who wishes to pursue the subject in more than the most superficial way. The first hundred and ninety pages of the book deal interestingly with such general matters as ecology, morphology, physiology and reproduction; the remainder of the book is a systematic discussion of protozoa. The innumerable excellent drawings are an outstanding feature.

Virus as Organism: Evolutionary and Ecological Aspects of Some Human Virus Diseases. By Frank MacFarlane Burnet, M.D., F.R.S. Harvard University, the Edward K. Dunham Lectures for the Promotion of the Medical Sciences, 1944. Harvard University Monographs in Medicine and Public Health [Number 8]. Price, \$2. Pp. 134. Cambridge, Mass.: Harvard University Press, 1945.

The subtitle of this book, "Evolutionary and Ecological Aspects of Some Human Virus Diseases," summarizes the contents. The first three chapters discuss reproduction, variation and survival of viruses in general, evolution and change in virus disease and the reaction of the host to virus infection. Several important virus diseases are discussed from the point of view of the ecologic interaction of the two species, virus and man. Dr. Burnet concludes that each of these diseases has its own individuality and must be studied in detail as far as practical measures are concerned. The possibilities in speculation about the origin of viruses are discussed. The dominant view seems to be that they evolve by parasitic degeneration from larger micro-organisms, probably bacteria.

The book is of particular interest to workers in virus research and to public health administrators. There is a bibliography of one hundred and twenty articles.

The Osseous System: A Handbook of Roentgen Diagnosis. By V. W. Archer, M.D. Price, \$5.50. Pp. 320, with 148 plates. Chicago: The Year Book Publishers, Inc., 1945.

This handy book covers in a comprehensive manner roentgenology of the osseous system. The left hand pages contain the text, and the right hand pages, reproductions of roentgenograms. These photographs, though small, are good reproductions and seem to illustrate well the points brought out in the text. The book should be useful not only to radiologists but also to general physicians.

Oral Medicine. By Lester W. Burket, D.D.S., M.D. Price, \$12. Pp. 674. Philadelphia: J. B. Lippincott Company, 1946.

The author of this book, widely experienced in the medical aspects of dentistry, has undertaken to bring together under one cover the oral manifestations of practically all the diseases to which the human body is heir. The result is a scholarly, readable, well documented and beautifully illustrated work which no dentist can afford not to read and which will be a valuable reference for physicians wishing to identify obscure lesions of the mouth or desiring to review all possible oral manifestations of systemic diseases.

After introductory chapters on medicodental relations, oral consultation and general laboratory procedures, the author begins a series of sections, the first of

which covers diseases generally considered intrinsic to the mouth, such as oral fusospirochetosis, heavy metal stomatitis, lingual diseases and gingivitis and the oral aspects of dermatology. Then follow sections on the general medical diseases, grouped under the headings organ systems, metabolism and infectious granulomas.

One might take issue with many statements in the book, such as one on page 227, in which the author, in speaking of angina pectoris, said, "This syndrome may precede typical coronary artery disease" and one on page 234, in which it is stated that stenosis of the pulmonary veins occurs in the tetralogy of Fallot. The color atlas consists of sixty well selected and beautifully reproduced photographs. The book should prove invaluable to dentists as a review of clinical medicine and it is an excellent source of information on oral aspects of disease for the physician.

News and Comment

ANNUAL CONVENTION OF THE AMERICAN ACADEMY OF ALLERGY

The American Academy of Allergy will hold its annual convention at Hotel Pennsylvania, New York city, November 25 to 27, inclusive. All physicians interested in allergic problems are cordially invited to attend the sessions as guests of the Academy without payment of a registration fee. The program has been arranged to cover a wide variety of conditions in which allergic factors may be important. Papers will be presented dealing with the latest methods of diagnosis and treatment, as well as with the results of investigation and research. Advance copies of the program may be obtained by writing to the Chairman on Arrangements, Dr. Horace S. Baldwin, 136 East 64th Street, New York City, before November 10.

APPOINTMENTS

Dr. Richard A. Kern, formerly professor of clinical medicine and chief of the outpatient department and the allergy section of the Hospital of the University of Pennsylvania, has been appointed professor and head of the department of medicine, Temple University School of Medicine, Philadelphia, to succeed Dr. Charles L. Brown.

CORRECTION

In the article by Dr. Norman Rosenthal, Dr. Sidney P. Zimmerman and Dr. Shepard Shapiro entitled "Prothrombin Level of Peripheral Blood and Sternal Marrow" in the April issue (*ARCH. INT. MED.* 77:420, 1946), "not" was inadvertently inserted in the first paragraph of the "Conclusions." The paragraph should read as follows:

"From the evidence presented we are led to conclude that prothrombin is not elaborated by the reticuloendothelial system and therefore is probably a function of the hepatic parenchyma."

PATHOGENESIS OF CIRRHOSIS OF THE LIVER OCCURRING IN PATIENTS WITH DIFFUSE TOXIC GOITER

ELI MOSCHCOWITZ, M.D.

NEW YORK

FROM THE standpoint of morphology, the liver has received abundant attention in fatal cases of diffuse toxic goiter. The lesions found are various; there are fatty changes, parenchymatous degeneration, venous congestion and, finally, cirrhosis of such a distinctive character as to be pathognomonic of this disorder. These lesions occur singly or in various combinations. In an appreciable percentage of cases no lesion of the liver is found. Acute yellow atrophy has been reported by Raab and Terplan,¹ Kerr and Rusk,² Zeldenrust and van Beek³ and Beaver and Pemberton.⁴ Foci of necrosis have been reported by Beaver and Pemberton,⁴ Habán,⁵ Rössle⁶ and Cameron and Karuntaratne.⁷ Whether focal necrosis represents an early or an abortive phase of acute yellow atrophy is questionable. Beaver and Pemberton found focal necrosis in 6.5 per cent of the livers of 107 patients afflicted with diffuse toxic goiter; in 5 patients the necrosis was of sufficient intensity to be deemed acute yellow atrophy. In my series of 31 cases, foci of necrosis were found in only 1, approximately 3 per cent. This

From the laboratories, Department of Pathology, the Mount Sinai Hospital.

1. Raab, W., and Terplan, C.: *Morbus Basedowii mit subakuter Leberatrophie*, *Med. Klin.* **19**:1154, 1923.

2. Kerr, W. J., and Rusk, G. Y.: *Acute Yellow Atrophy Associated with Hyperthyroidism*, *M. Clin. North America* **6**:445, 1922.

3. Zeldenrust, J., and van Beek, C.: *Morphologischer und experimenteller Beitrag zur Pathogenese der Leberveränderungen bei Morbus Basedowi*, *Beitr. z. path. Anat. u. z. allg. Path.* **103**:568, 1939.

4. Beaver, D. C., and Pemberton, J. deJ.: *Pathological Anatomy of the Liver in Exophthalmic Goitre*, *Ann. Int. Med.* **7**:687, 1933.

5. Habán, G.: *Ueber die Leberveränderungen bei Morbus Basedowii mit besonderer Berücksichtigung der Lebercirrhose*, *Beitr. z. path. Anat. u. z. allg. Path.* **92**:88, 1933.

6. Rössle, R.: *Ueber die Veränderungen der Leber bei der Basedowschen Krankheit und ihre Bedeutung für die Entstehung anderer Organsklerosen*, *Virchows Arch. f. path. Anat.* **291**:1, 1933.

7. Cameron, G. R., and Karuntaratne, W. A. E.: *Liver Changes in Exophthalmic Goitre*, *J. Path. & Bact.* **41**:267, 1935.

necrosis was associated with cirrhosis typical of that found in cases of diffuse toxic goiter, but topographically the two lesions were independent. Other observers of cirrhosis in cases of diffuse toxic goiter do not report focal necrosis. Apparently focal necrosis is a rather unusual finding, and my reason for commenting on it is that some physicians regard the cirrhosis as arising from necrotic foci. I do not agree with this point of view.

In this study I shall be concerned only with a consideration of the cirrhosis.

Although disturbances of hepatic function play only a subordinate role in cases of diffuse toxic goiter, the study of the pathogenesis of this peculiar type of cirrhosis is of interest not only for its own sake but also for the important implications which it bears concerning the mechanism of some of the clinical cardiovascular disturbances commonly found in patients with diffuse toxic goiter.

HISTORICAL REVIEW

One of the earliest reports of cirrhosis occurring in patients with diffuse toxic goiter is that of Marine and Lenhardt,⁸ who found atrophic cirrhosis in 4 of 6 patients; in all 4 the "exophthalmic goiter" was of long standing. They found small livers, sometimes smooth, sometimes slightly granular or distinctly hobnailed. The connective tissue content was increased and varied from slight thickening of the portal spaces to well marked fibrous bands. In 1930 Warthin,⁹ in a study of the hepatic lesions in cases of "exophthalmic goiter," found in some instances a peculiar form of parenchymatous hepatitis, characterized by lymphocytic infiltration, bile duct proliferation and an increase of the connective tissue stroma of the portal spaces sufficient in his eyes to make the diagnosis atrophic cirrhosis. Warthin recognized that the lesion differs from the typical Laennec cirrhosis in that the new connective tissue is intralobular and irregularly distributed. Attention was first sharply focused on the cirrhosis in cases of diffuse toxic goiter by Rössle's¹⁰ publication in 1933. Since then publications of studies of this lesion have been more numerous. Rössle ascribed the pathogenesis of the cirrhosis to "serous hepatitis" of toxic origin, a lesion which he had described many years before¹⁰ as the essential primary phenomenon of the conventional type of Laennec cirrhosis. The lesion begins with accumula-

8. Marine, D., and Lenhardt, C. H.: *Pathological Anatomy of Exophthalmic Goitre*, Arch. Int. Med. 8:265 (Sept.) 1911.

9. Warthin, A. S.: *Hepatic Lesions Associated with Exophthalmic Goitre*, Ann. Int. Med. 4:501, 1930.

10. Rössle, R.: *Die Veränderungen der Blutkapillaren der Leber und die Bedeutung für die Histogenese der Lebercirrhose*, Virchows Arch. f. path. Anat. 188:484, 1907.

tion of fluid in the Disse spaces, a pericapillary edema, with disintegration of the capillaries, resulting in hyperemia and occasional hemorrhages or formation of "blood lakes"; there is disassociation of the liver cells, which may be vacuolated or may stain faintly. In the later phases new collagenous fibrils are laid down in the Disse spaces. Rössle did not regard this new formation of fibrils as inflammatory, because it occurs without the intermediacy of granulation tissue, and he cited in explanation the work of Doljanski and Roulet,¹¹ who found that in cultures of cells collagenous fibrils were deposited in the plasma far away from the new cellular formation. In the further development of the cirrhotic process the new connective tissue increases and encloses smaller or larger fragments of hepatic trabeculae, which often undergo new bile duct formation. In this concept the capillary toxicosis is primary and the changes in the parenchyma are secondary. Rössle correctly emphasized the striking predilection of the process for the subcapsular areas of the liver. He ascribed this predilection to the fact that toxic substances are more liable to affect this region and cited the observation of Laird,¹² who injected sodium iodide and phosphorated oil into the portal vein and found these substances most abundant in the subcapsular region.

Habán in the same year⁵ reported cirrhosis in 10 of 26 patients who died of "Basedow's disease." Like Rössle, he found the increase of connective tissue most marked beneath the capsule, from which strands penetrate the parenchyma to a greater or lesser extent. He found accretion of connective tissue only rarely in other areas of the organ. He noted the angiomatous dilatation of the vessels and the islets of liver cells within the cirrhotic areas, which may undergo bile duct transformation. The new connective tissue conspicuously differs topographically from that noted in Laennec cirrhosis in that the areas are star shaped and do not intercommunicate. The new connective tissue varies in the degree of cellularity and includes mostly lymphocytes, occasionally plasma cells and a few polymorphonuclear leukocytes. He viewed the genesis as connective tissue replacement of previous necrosis. He offered no explanation for the subcapsular predilection.

Weller¹³ also in 1933, in a study of the hepatic changes in cases of "exophthalmic goitre," found patchy parenchymal interlobular hepatitis in 26 of 48 cases, characterized by lymphocytic infiltration, bile duct formation and increased stroma in the capsule of Glisson. He noted

11. Doljanski, L., and Roulet, F.: Studien über die Entstehung der Bindegewebsfibrille, *Virchows Arch. f. path. Anat.* **291**:260, 1933.

12. Laird, E. G.: Peritoneale Resorption mit besonderer Berücksichtigung der Wirkung auf die Leber und die Resorptionswege zur Leber, *Virchows Arch. f. path. Anat.* **291**:440, 1933.

13. Weller, C. V.: Hepatic Lesions Associated with Exophthalmic Goitre, *Tr. A. Am. Physicians* **45**:71, 1930; *Hepatic Pathology in Exophthalmic Goiter*, *Ann. Int. Med.* **7**:543, 1933.

that many of the portal spaces were intact and that there was an intralobular connective tissue invasion of the periphery of the lobules—attributes that differentiated this form of cirrhosis from the Laennec type. He regarded the lesion as toxic and not cardiac because the new connective tissue was not around the central veins.

Beaver and Pemberton⁴ in 1933-1934 reported the hepatic changes in 107 fatal cases. They found two outstanding types of changes: (1) acute, characterized by fatty metamorphosis and central and focal necrosis; (2) chronic, which is again subdivided into (a) simple atrophy and (b) toxic subacute atrophy which in some instances progressed to actual cirrhosis. They attached little importance to the fatty changes because such changes occur in a wide variety of other conditions, although to an appreciably less degree than in diffuse toxic goiter. The livers that showed simple atrophy without cirrhosis showed little; but significantly, to me at least, the authors described streaks or bands of connective tissue within the lobule, around the periportal spaces or extending between two periportal spaces. They regarded these changes as the result of simple parenchymal atrophy, possibly of degeneration, but their findings resemble so closely, topographically at least, those found in my cases that they might be regarded as already representing early cirrhosis. Beaver and Pemberton reported 64 cases of cirrhosis, mild in 48 and severe in 16. Microscopically, they noted a variability of the localization of the new connective tissue. The largest amounts were around the periportal spaces, encroaching on the periphery of the lobule. In other instances the connective tissue occurred throughout the lobule or around the central veins or as threadlike bands extending between the central and the portal veins or between two portal spaces. The new connective tissue contained lymphocytes and new bile ducts. Regeneration was not a prominent feature. They regarded the genesis as toxic, in part the result of simple atrophy. The lesions revealed various grades; in most instances they were progressive, corresponding morphologically to subacute or early chronic toxic atrophy of the liver.

Cameron and Karuntaratne⁷ in 1935 described three types of morphologic change in the liver in cases of "exophthalmic goitre": (1) acute damage (marked fatty change and/or foci of necrosis); (2) progressive damage (various stages of cirrhosis); (3) arrested damage (nodule formation, atrophy). Of 30 cases, 10 showed cirrhosis, in 3 of which the insular type, in 4 the interinsular type and in 3 the annular type was represented. The microscopic descriptions are so sketchy that one cannot determine the precise morphologic character of the lesions. Apparently, the insular type refers to a lesion in which there is lymphocytic infiltration of the portal spaces. Whether this change may be classified as cirrhosis is questionable. The interinsular and the

annular types represent the characteristic cirrhosis of diffuse toxic goiter. The authors submitted no explanation of the pathogenesis. Zeldenrust and van Beek³ reported a case in 1939. The cirrhosis was mostly subcapsular; there was venous congestion; the endothelium of the hepatic capillaries was loosened, and erythrocytes were found in Disse spaces. The authors viewed this "serous hepatitis" as secondary and not primary. They were the first to regard the genesis of the lesion as cardiac but submitted no reasons therefor.

Schaffer¹⁴ in 1940, in a study of 24 cases of "hyperthyroidism," found cirrhosis in 6—advanced in 2 and moderate in 4. The cirrhosis was characterized by degenerative changes leading to atrophy of the hepatic cells and by a chronic inflammatory reaction occurring peripherally in the altered lobules, with regeneration of an imperfect type. Schaffer also noted "local interstitial hepatitis," characterized by lymphocytic infiltration of the periportal areas, in 83 per cent of the cases. In a control series he found identical changes in about 25 per cent. He did not regard the lesion as cardiac in origin.

OBSERVATIONS IN THIRTY-ONE CASES OF DIFFUSE TOXIC GOITER

Incidence of Cirrhosis.—Of 31 patients who died in Mount Sinai Hospital between the years from 1930 to 1944 and whose disease was diagnosed as diffuse toxic goiter, or exophthalmic goiter, during life, 11 had cirrhosis—an incidence of 35.5 per cent. This accords with 38.8 per cent found by Habán⁵ in 26 cases of "exophthalmic goitre."

Sex Distribution of Cirrhosis.—Of the livers showing cirrhosis, 5 were from males and 6 from females. Of the total of 31 patients who died with the diagnosis of exophthalmic goiter, 20 were females and 11 males. The percentage of males with cirrhosis is higher than that conventionally regarded as the average. The significance of this difference is not apparent at this time.

Duration of the Syndrome.—As diffuse toxic goiter is a hyperkinetic disease,¹⁵ it is sometimes difficult to judge the precise duration. This can be gaged with fair accuracy when the disease follows a sudden emotional crisis, but in most instances the onset is gradual, so that the patient's statement is only roughly approximate. Despite these shortcomings, it is apparent that, by and large, the incidence of cirrhosis bears a relation to the duration of the disease. Of 10 patients with cirrhosis from whom a history of the duration of the disease was

14. Schaffer, J. M.: Disease of the Liver in Hyperthyroidism, Arch. Path. 29: 20 (Jan.) 1940.

15. Moschcowitz, E.: The Hyperkinetic Diseases, Am. J. M. Sc. 206:576, 1943.

obtained, all but 2 revealed a duration of two years or more. In 5 patients the duration was between three and ten years. One stated that the duration was "over one year," and another that it was "more than two years." One said that the disease had lasted for "many years." Only 2 patients had been aware of the syndrome for less than one year.

Of the 20 patients without cirrhosis, 3 did not mention the duration of the disease, and 12 had been affected for a year or less. Two others had been cured of their thyroid malady by thyroidectomy ten years previously; one of these died of congestive failure due to coronary disease and the other of peritonitis following perforation of an ulcer of the sigmoid flexure. One of the remaining 3, all of whom presented evidences of diffuse toxic goiter both clinically and anatomically (as manifested by hyperplasia of the thyroid gland), died of congestive failure due to hypertensive disease; 2 revealed coronary arteriosclerosis and chronic congestion of the viscera, and died in "thyroid storms." Although the figures are only approximate, the average duration of the syndrome was three and a half years in patients with cirrhosis and eight months in those without cirrhosis. It is apparent that there is a definite relation between the duration of the disease and the incidence of cirrhosis. This is in accord with the experiences of Marine and Lenhardt,⁸ Schaffer,¹⁴ Cameron and Karuntaratne,⁷ Beaver and Pemberton⁴ and Habán.⁵ However, the relation is not absolute since 2 of the patients with cirrhosis had diffuse toxic goiter one and four months, respectively, while 5 of those without cirrhosis had it for one or more years and 3 for five, eight and fourteen years, respectively. The reasons for the absence of cirrhosis will be discussed in a later portion of this communication.

Age.—It is noteworthy that in the postmortem experience at Mount Sinai Hospital the patients dying with evidence of diffuse toxic goiter have been mostly in the sixth decade of life. The average age of the 31 patients was 54.4 years; the youngest was 23 and the oldest 80 years of age. The average age of those in whom cirrhosis was revealed was 51.2 years; the youngest was 30 and the oldest 65. Of those without cirrhosis, the average age was 56.1 years; the youngest patient was 23 and the oldest 80. The difference between these two groups is not sufficient to be of significance.

This high age incidence, in my experience, can be ascribed first to the greater risk of operation in the older age group. The majority of these patients died after a postoperative "thyroid storm"; furthermore, a large number died during the years when preoperative administration of strong solution of iodine U. S. P. was not routine. A lesser number died of postoperative pneumonia. Second, cardiac failure following long-standing diffuse toxic goiter is exceedingly common during

the senescent years, as shown by the fact that about a third of these patients died with clinical and anatomic evidences of congestive failure.

Pathologic Changes in the Liver.—(a) Macroscopic Examination: The gross appearance of the livers which revealed cirrhosis varied, depending on the stage of the process. In the early phases the liver appears normal, with a smooth glistening capsule, and reveals firm consistency; the cut section shows the normal lobular structure, modified as the case may be by the presence and the intensity of fatty or parenchymatous degeneration or by venous congestion. In the later phases the surface of the liver may be granular or even nodular, a change involving the entire surface or, more commonly, circumscribed to one or more areas on either the superior or the inferior surface.

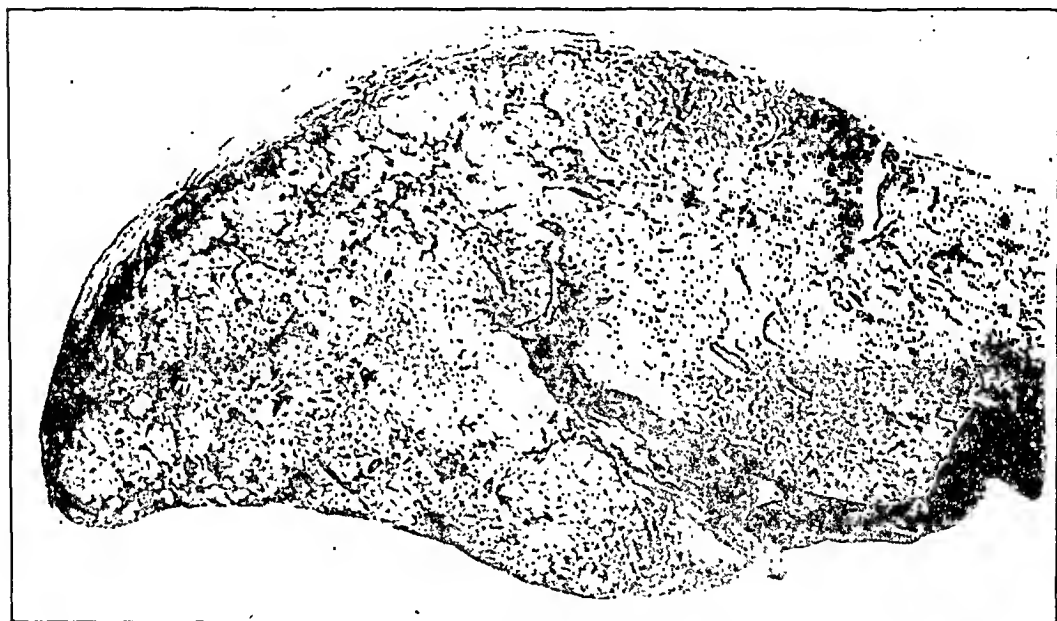


Fig. 1.—Gross appearance of the cirrhotic liver of a patient with diffuse toxic goiter, showing the subcapsular predilection of the fibrosis. This illustration is taken from Rössle.⁶

The capsule of the liver is sometimes appreciably thickened. The consistency of the organ is more dense, and it cuts with increased resistance. The cut surface reveals a trabeculated appearance, with nodules varying from 1 to 4 mm. in diameter and surrounded by firm fibrous tissue. Especially striking, as Rössle pointed out, is the prominence of these cirrhotic areas in the subcapsular zone; in 2 instances the process was limited strictly to this area (fig. 1). The weight of the liver averaged 1,200 Gm., varying between 890 and 1,800 Gm. According to Krieger,¹⁶ the normal weight varies between 1,659 and 1,786 Gm. The diminution of size cannot be entirely

16. Krieger, M.: Ueber die Atrophie der menschlichen Organe bei Inanition, Ztschr. f. ang. Anat. 7:87, 1920.

ascribed to the cirrhosis, since it is well known that patients with diffuse toxic goiter are usually below normal in weight and the weight of the liver decreases correspondingly. Inasmuch as sufficient data were not available in regard to the weights of the patients at death, I cannot say whether the weight of the liver as compared with the total body weight corresponds to the percentage, 2.69, which Krieger determined for the liver of the normal subject. Moreover, the weight of the liver is additionally modified by the amount of the contained blood, a congested liver weighing more than the average before the blood is expressed. As a matter of fact, the larger weights in the present series were those of livers in which venous congestion was associated.

The gross vessels of the liver did not reveal any abnormality. The gallbladder contained a calculus in 1 instance; it appeared normal in all other instances.

(b) Microscopic Examination: Superficial inspection reveals patches of fibrosis scattered apparently haphazardly throughout the hepatic lobule with no particular relation to any of the normal anatomic landmarks in the lobule, namely, the portal spaces or the central or the hepatic veins (fig. 2 A). These areas are usually wedge shaped and vary in size from those which occupy only a portion of a lobule to some that involve an entire lobule or a number of lobules. Often they are confluent and then they assume a stellate appearance (fig. 2 B). Within the larger areas apparently intact portal spaces are still visible. In accord with the macroscopic appearance, the subcapsular areas are predominantly involved, while the deep portions of the parenchyma are involved to an appreciably lesser extent. In a few instances the morbid changes were exclusively limited to the subcapsular area. Furthermore, the fibrotic areas are not scattered haphazardly but are often prolonged from the portal spaces either directly into the parenchyma of the lobule or, more commonly, directly into the vascular septums between the lobules. This intimate relationship between the portal spaces and the cirrhotic areas is confirmed in serial sections when one finds that a fibrotic area, apparently without demarcation, can be shown to arise from a neighboring portal space (fig. 3). The stellate areas of cirrhosis are the resultant of the projection from two or more portal spaces. Curiously, these areas of fibrosis arise usually from only the smaller divisions of the portal spaces, the larger ones being uninvolved. Not all the portal spaces are involved, and this is noted especially in the deeper portions of the parenchyma. When the fibrotic areas are followed peripherally from their origin in the portal spaces, many are seen to pass directly into the central vein or more commonly into the collecting veins (fig. 4) (*Sammelvene*, Pfuhl¹⁷). These collecting veins repre-

17. Pfuhl, W., in von Möllendorff, W.: *Handbuch der mikroskopischen Anatomie des Menschen*, Berlin, Julius Springer, 1932, vol. 5, pt. 2.

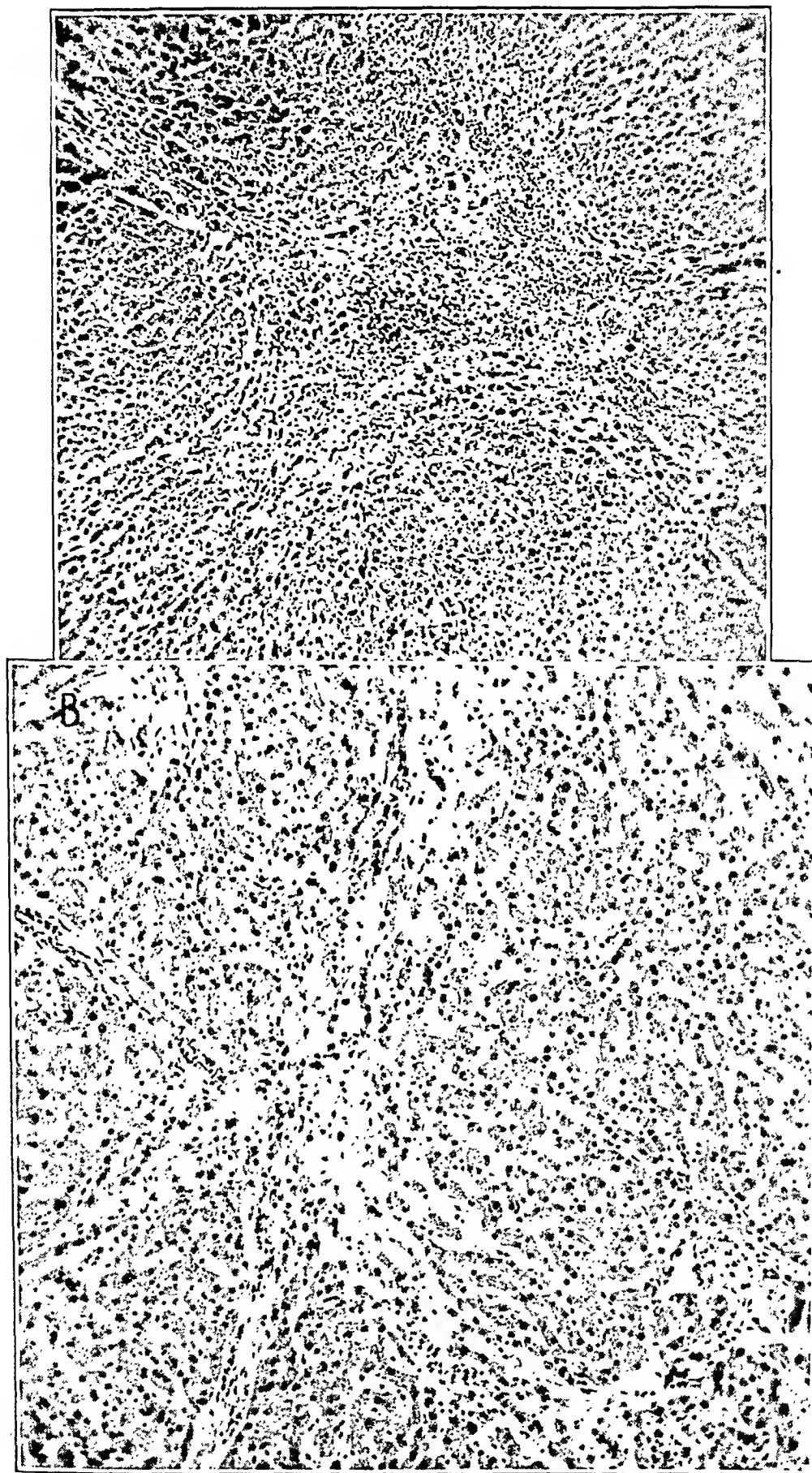


Fig. 2.—*A*, typical area of fibrosis apparently unrelated to any portal space, central vein or hepatic area. *B*, area of fibrosis presenting a stellate conformation.

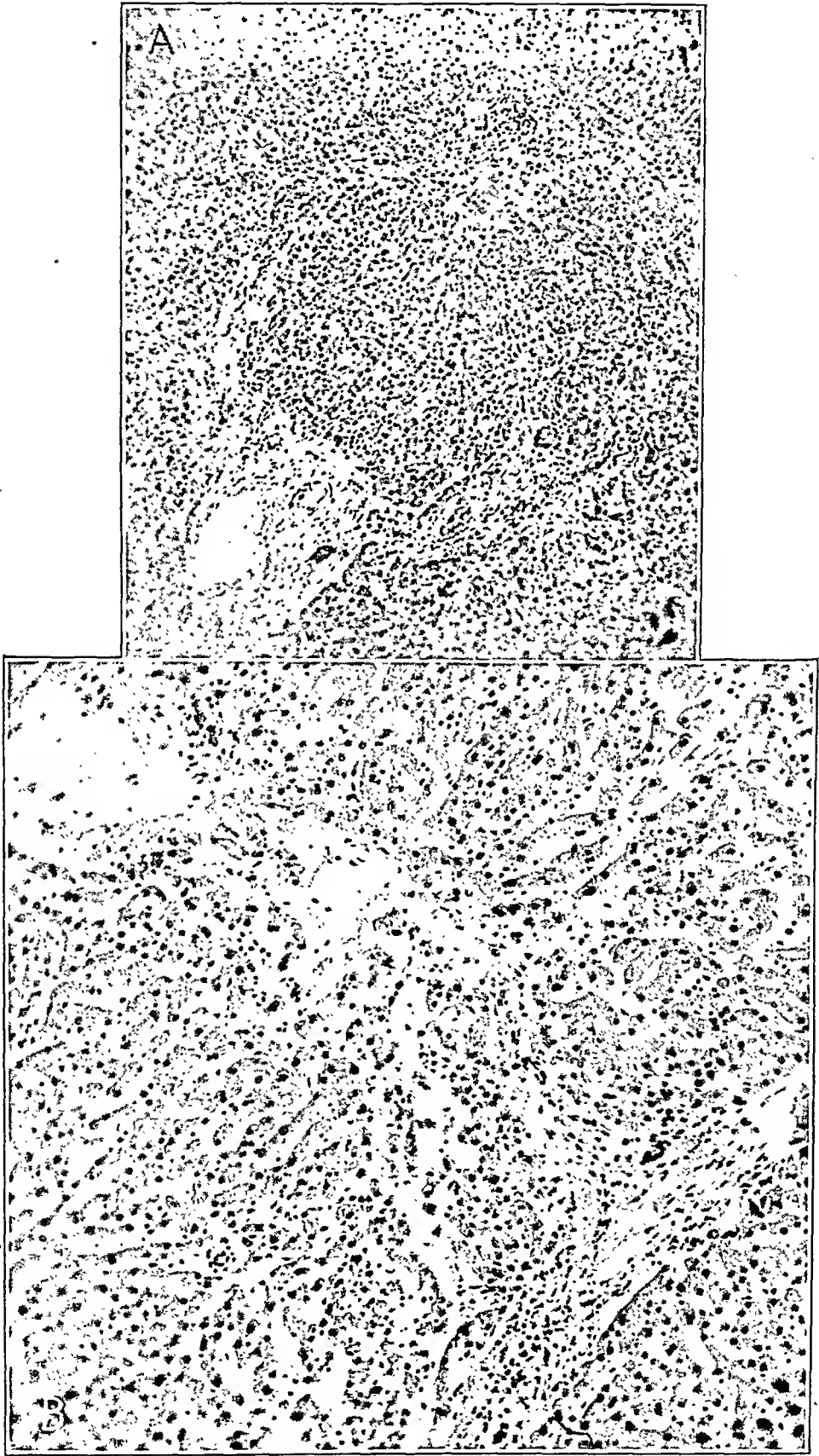


Fig. 3.—*A*, fibrosis arising from a small portal space and penetrating into interlobular spaces. *B*, terminal picture of serial sections showing fibrosis penetrating the interlobular space and there breaking up into dilated sinusoids.

sent the maturer forms of the central veins and are formed by the aggregation of a number of lobules into one unit, an arrangement which, according to Pfuhl (fig. 5), is the usual anatomic arrangement in the human liver.

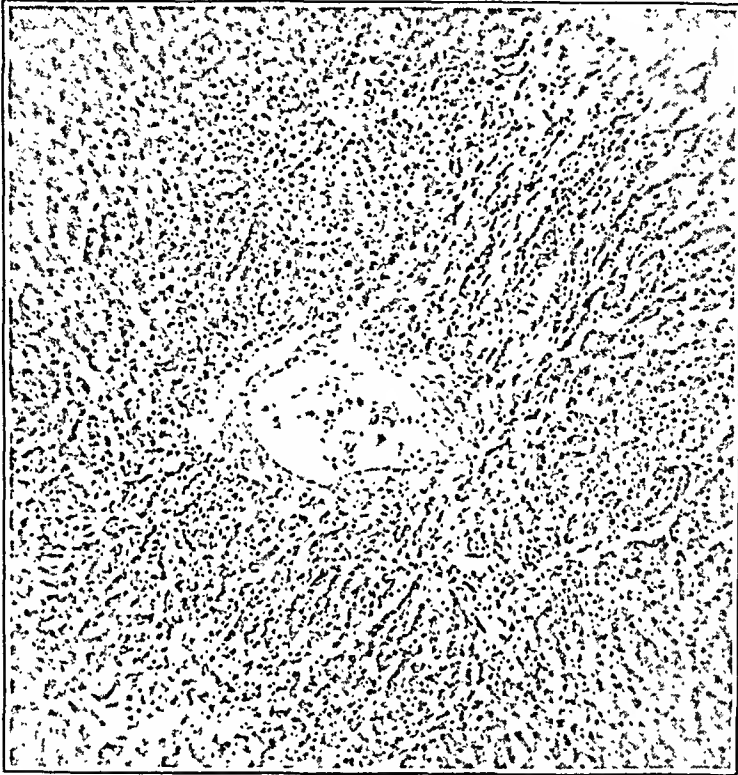


Fig. 4.—An area of fibrosis showing dilated sinusoids entering a central or a collecting vein (*Sammelvene*).

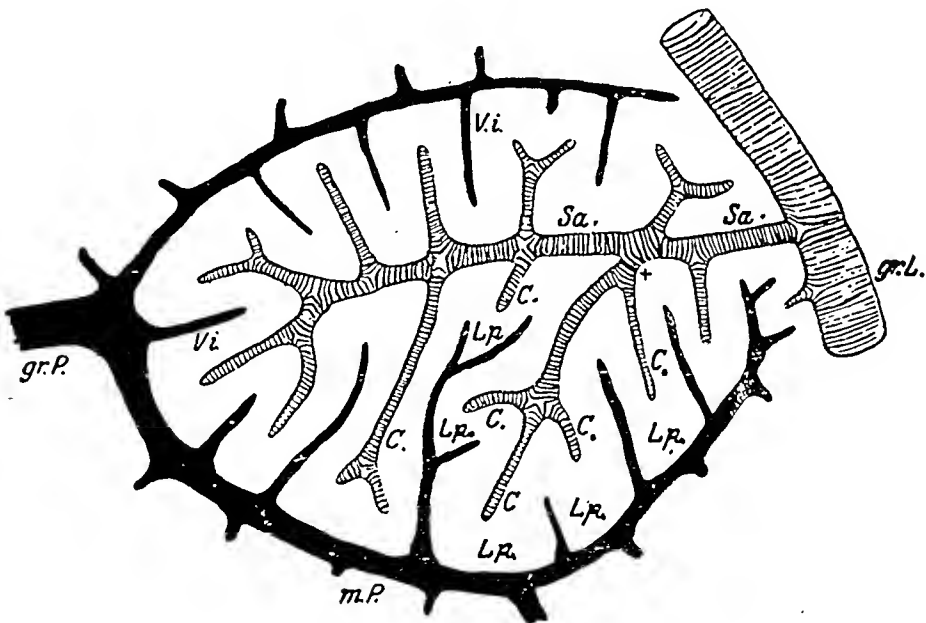


Fig. 5.—Scheme of a normal hepatic lobular cluster: *gr. P.*, large portal branch; *Vi.*, interlobular vein; *Lp.*, lobule; *C.*, central vein; *Sa.*, collecting vein (*Sammelvene*); *gr. L.*, large hepatic vein. (The scheme is taken from Pfuhl.¹⁷)

I have not noted the complete encirclement of a lobule by the newly formed connective tissue so characteristic of Laennec cirrhosis. One notes at the most the isolation of a portion of the hepatic lobule.

The finer microscopic structure depends on the stage of the process. In the early phase the sinusoids are strikingly widened. The hepatic cell cords reveal more or less complete dissociation and consist of one or more cells embedded in a system of intercommunicating sinusoids

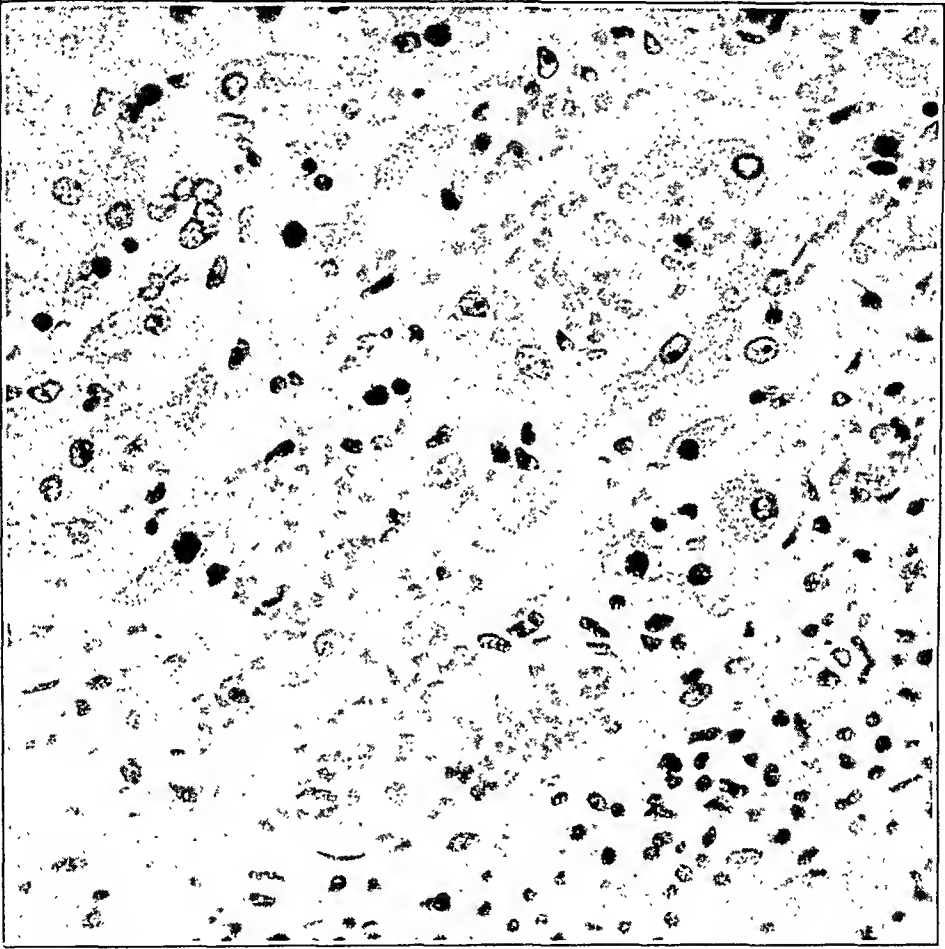


Fig. 6.—Early phase of the lesion showing dilated sinusoids and dissociated, compressed trabeculae.

or vascular spaces (fig. 6). The cords are usually much narrowed and deformed and contain blood pigment. In the unaffected hepatic areas the cells contain no pigment whatever. On the other hand, it is of interest that with stains for glycogen the dissociated liver cells contain none while nearly all the cells of the normal cords stain positively. The much dilated sinusoids are filled with blood and are surrounded by fine fibrils of collagen, and with silver stains, even in the early stages there is a condensation of fibrillar connective tissue within these dilated

sinusoids (fig. 7). At times the sinusoidal spaces are so wide as to be aptly called "blood lakes." One can also note, even at this stage, greater or lesser infiltration with round cells, limited entirely to these areas.

In the later stages the dilated sinusoids become progressively surrounded by fibrillar connective tissue, in which large numbers of round cells are interspersed. The new connective tissue surrounds a vast

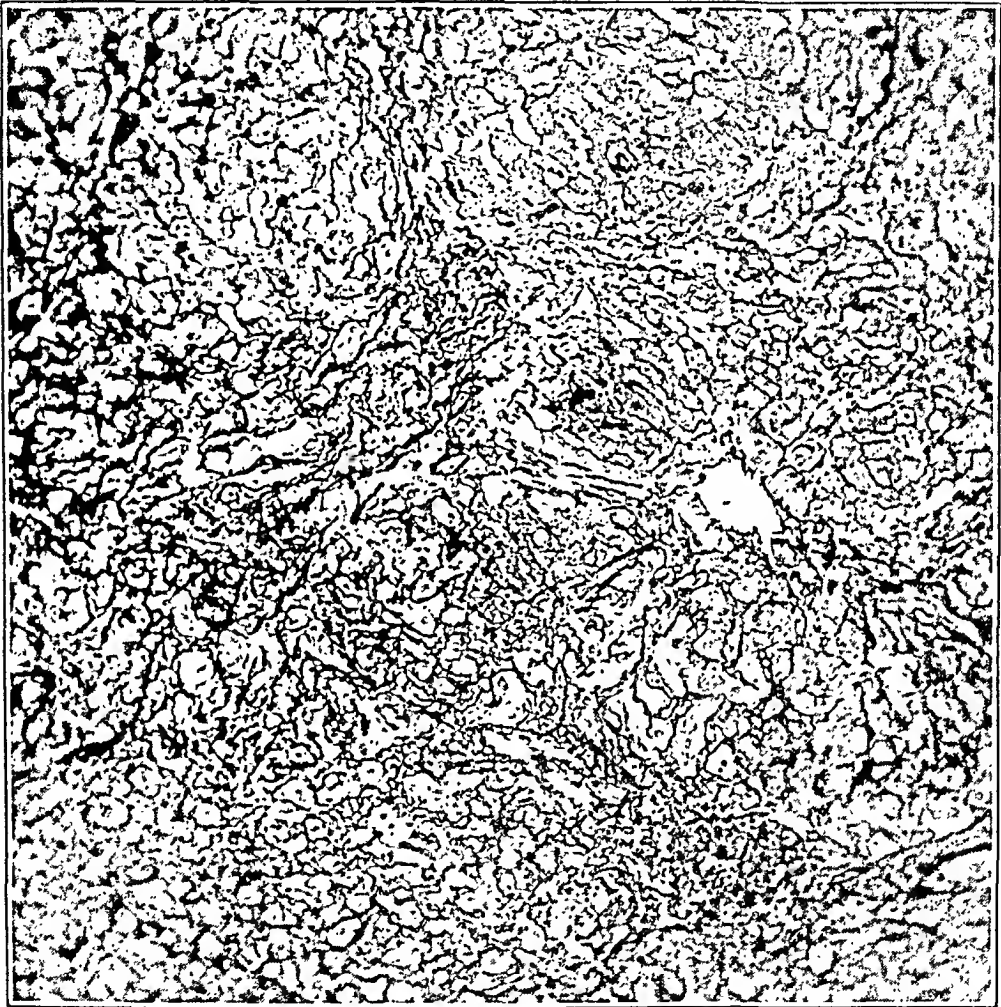


Fig. 7.—Silver stain of a fibrotic area showing condensation of fibrillar connective tissue.

number of vascular spaces varying from those of capillary size to those of the dimensions of an arteriole, resulting in an angiomatous appearance (fig. 8). Within these areas are single cells or multiple cell remnants of liver cords in a greater degree of dissociation; many have even been transformed into newly formed "bile ducts."

If one is lucky enough to find a plane in which these cirrhotic areas can be traced back to their origins in the portal spaces or, better, if one can do this with the aid of serial sections, one notes an arteriole arising

from the portal space and penetrating directly into the cirrhotic area (figs. 9 and 10). In the earlier phases the end of the artery apparently breaks up into the widely dilated sinusoids or blood spaces. So uniformly is this observed that I deem it a distinctive morphologic characteristic of the cirrhosis accompanying diffuse toxic goiter, which suggests (as I shall later discuss) an explanation for the pathogenesis of the lesion. In the late stages the sclerosis is so dense as to obliterate

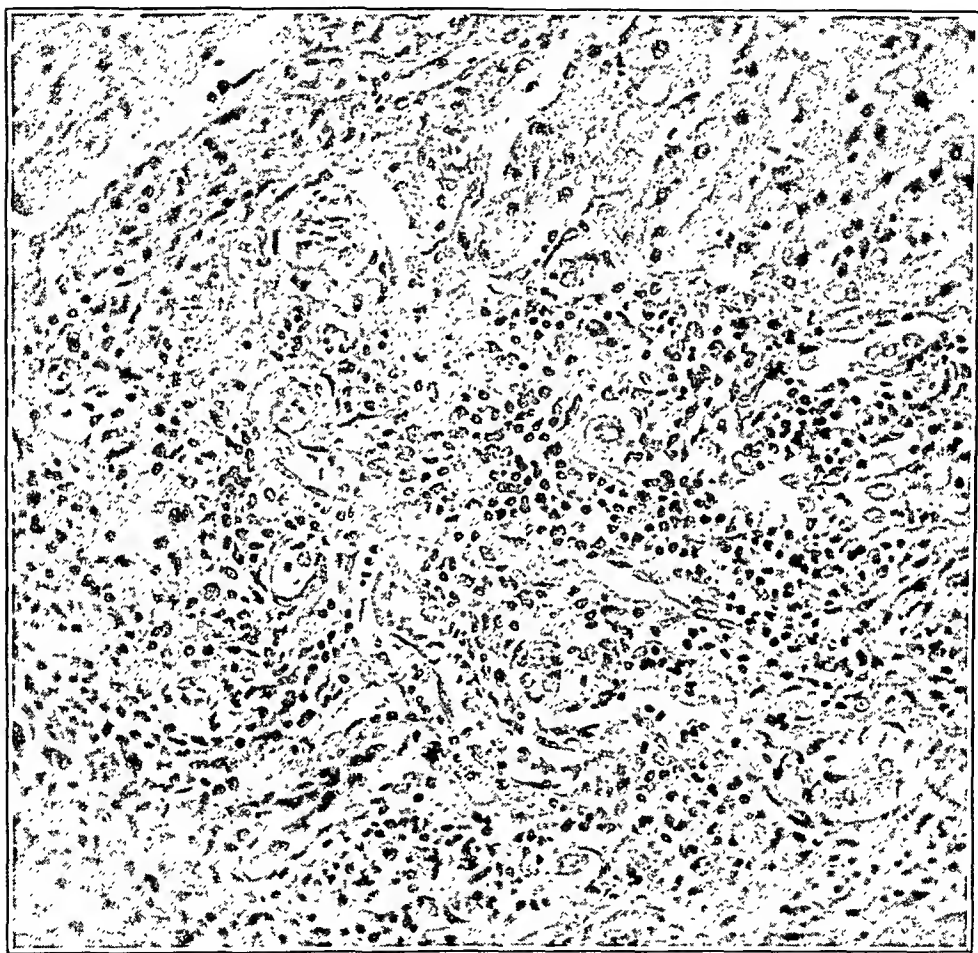


Fig. 8.—Late phase of the lesion showing round cell infiltration, fibrosis and angiomatous appearance.

the finer landmarks, and the relation of these patches to the artery is not so obvious.

The portal spaces aside from their relation to the cirrhotic areas vary morphologically. In most instances they show sparse to moderate round cell infiltration. Such infiltration is common, however, not only in noncirrhotic livers of patients with diffuse toxic goiter but also in livers of persons dying of other maladies. The round cell infiltration has therefore little significance. In many of the livers there was a

moderate increase of the connective tissue in the portal spaces. This was present both in the livers with and in those without cirrhosis. The increase was never sufficient to warrant the diagnosis of insular cirrhosis, and in a parallel series of livers removed from patients dying of other disorders the incidence and the amount of new connective tissue were practically the same.

The portal vein, the hepatic artery and the bile ducts appear normal. The capillaries within the portal spaces show no congestion. The capil-

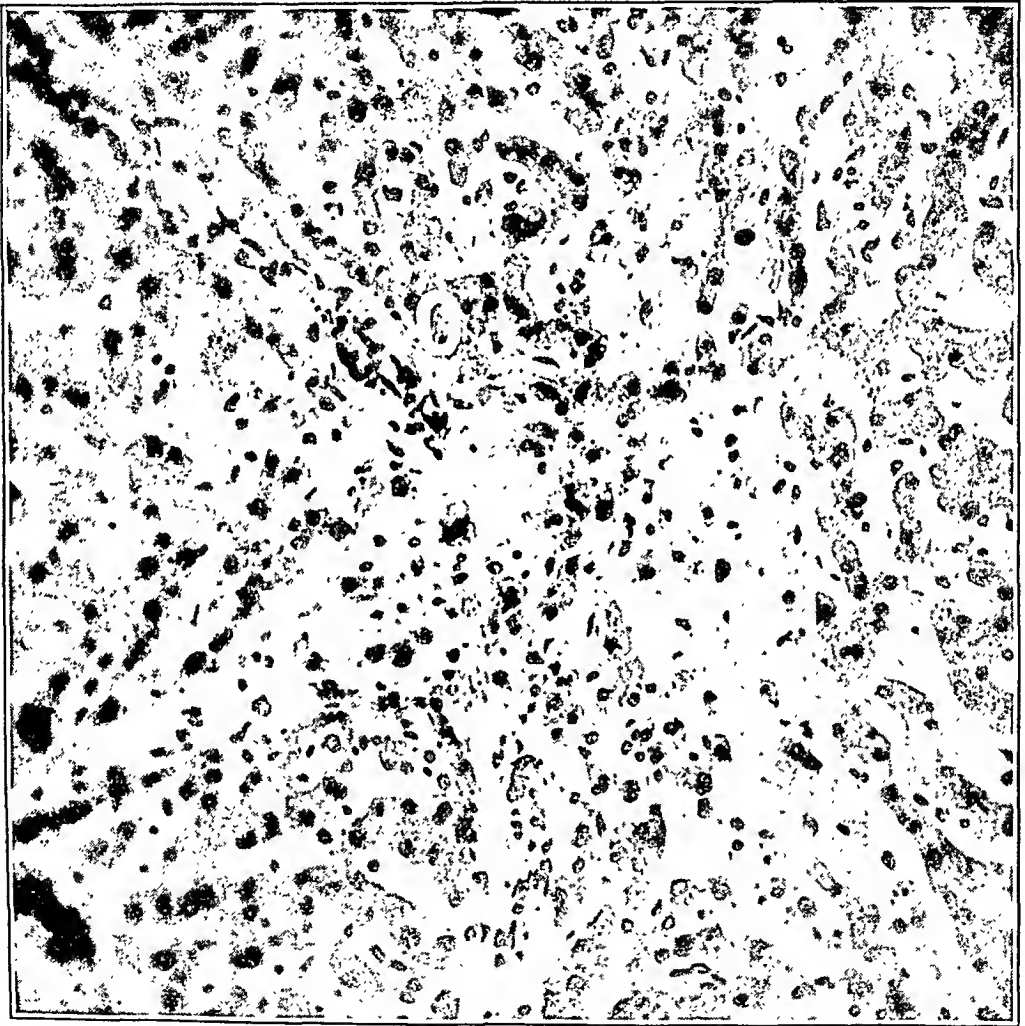


Fig. 9.—Arteriole (O) in a vascular septum penetrating into a fibrotic area with dilated sinusoids.

laries arising from the portal vein which penetrate into the interlobular vascular septums occasionally show some dilatation but otherwise reveal no abnormality.

The most common alteration of the parenchymal hepatic cells is a fatty infiltration varying from a slight to a fairly extensive process. It was present in 14 cases. Usually the fatty change is not particularly evident. In a control series of livers removed from patients with other

diseases this infiltration appears somewhat less common, and its intensity is of a lower grade. However, the range of fatty infiltration varies so widely that the distinguishing of the normal from the abnormal is difficult. In my series the fatty change was not more common in livers with than in those without cirrhosis, so that it is not significant in the genesis of the cirrhosis. In a few instances moderate parenchymatous degeneration was noted.

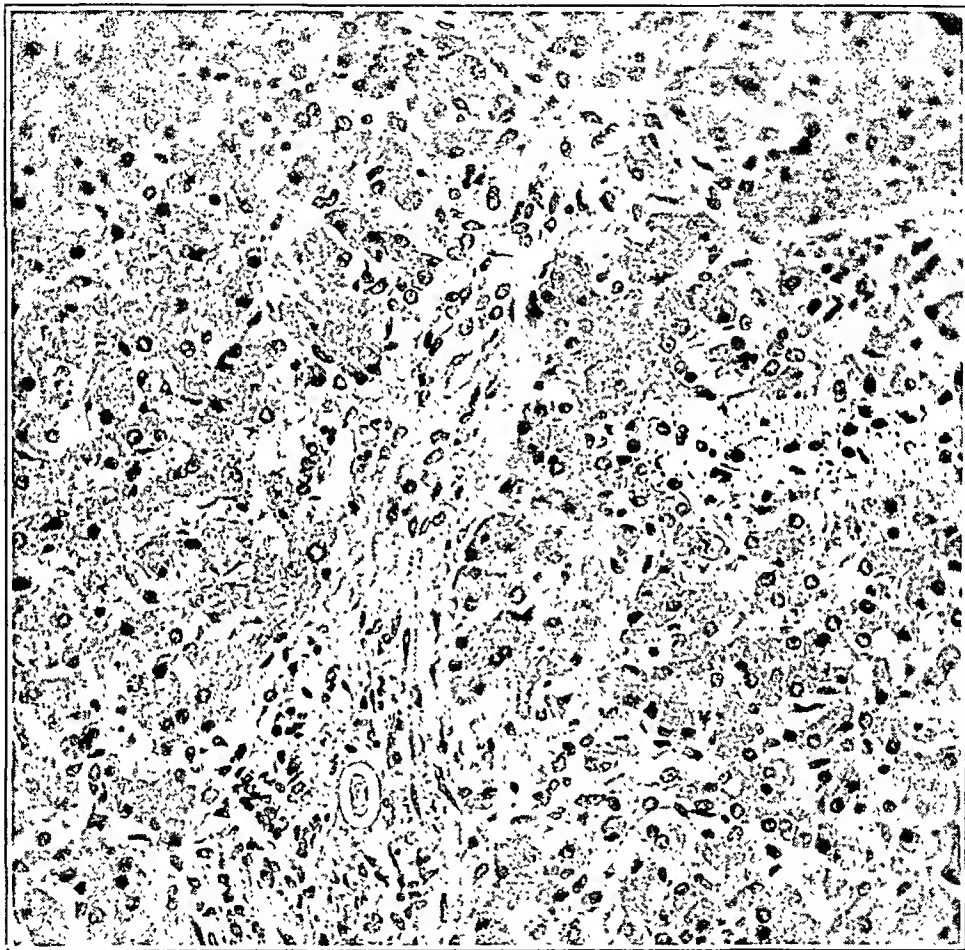


Fig. 10.—Arteriole (O) in a vascular septum in a fibrotic area.

Blood pigment, as I have already mentioned, was noted in the parenchymal cells lying within the cirrhotic areas, as well as around the central veins in the livers with associated chronic venous congestion. Although there was a patient who presented clinical jaundice terminally, no bile pigment was observed in the liver cells. In the liver of another patient there were a few small foci of necrosis, characterized by isolated groups of shadow cells that stained but faintly, in which there was a sprinkling of polymorphonuclear cells. This finding was associated with

cirrhosis, but the cirrhotic areas presented no topographic relation to these foci of necrosis.

The characteristic morphologic evidence of chronic venous congestion was found in 13 of 31 cases. In 3 the lesion was associated with cirrhosis. In the remaining 8 cases with cirrhosis there was no chronic venous congestion; in 10 cases chronic venous congestion was unassociated with any other lesion.

The capsule of the liver was normal except in the instances in which subcapsular cirrhosis was present; in these instances it showed slight to moderate thickening and sparse round cell infiltration. In 2 instances a tiny bile duct adenoma was found situated just beneath the capsule. In 1 case a small subcapsular angioma was present. The occurrence of these neoplasms is probably incidental.

"Serous hepatitis" like that described by Rössle¹⁰ was noted in 12 of the 31 cases, an incidence of 38.7 per cent, which is approximately that found by Keschner and Klemperer¹⁸ (43 per cent) in a series of livers of patients dying of diffuse toxic goiter. They also found "serous hepatitis" in 15 per cent of all patients dying from other causes. In my series this lesion was slightly more common in the patients with cirrhosis than in those without, in the proportion of 7 to 5. These facts alone would preclude "serous hepatitis" as the primary event in the causation of this type of cirrhosis. A lesion such as I have described, which is so characteristic of this disorder, cannot reasonably be the result of "serous hepatitis," which is so commonly found in other conditions. I have thus far not found this type of cirrhosis, whether viewed morphologically or topographically, in any other disease. The "serous hepatitis" must therefore be viewed as a secondary manifestation, a point of view also taken by Habán⁶ and Zeldenrust and van Beek.⁸

PATHOGENESIS

A clue is offered by the microscopic appearance of the earliest phase of the lesion and its progression. One finds a dilatation of capillaries so marked at times as to lead to focal hemorrhage, with compression and dissociation of the surrounding hepatic trabeculae, the cells of which almost invariably contain blood pigment. In the later phases there is a progressive increase of connective tissue around these dilated spaces, with abundant round cell proliferation and progressive development of the previously dilated capillaries to small venules, affording an angiomatous appearance of the new tissue. The further senescence is characterized by an increase in the amount and the density of the new connective tissue. In appearance and progression the lesion is identical

18. Keschner, H. W., and Klemperer, P.: Frequency and Significance of Hepatic Edema, *Arch. Path.* 22:583 (Nov.) 1936.

with that noted in chronic congestion of the liver and its later phase, cardiac cirrhosis. As I have tried to show,¹⁹ cardiac cirrhosis which arises in the presence of hypertension of the pulmonary circulation is due to venocapillary sclerosis consequent to the increased back pressure transmitted downward through the inferior vena cava into the hepatic veins, thence into the central veins and finally into the radiating sinusoids of the lobule. Cardiac cirrhosis is usually associated with sclerosis of the pulmonary artery and of the alveolar capillaries and with sclerosis of the hepatic veins.²⁰ The earlier lesion is the chronic congestive or nutmeg liver. The capillary sclerosis occurring in the hepatic lobule resembles closely that seen in certain organs of the greater circulation, especially notable in the glomeruli in hypertensive disease, and I have employed the term "arteriocapillary sclerosis" to the summation of this process. However, the cirrhosis which I have described differs in one fundamental aspect from the conventional cardiac cirrhosis, namely that topographically the lesion is never present around the central veins but is found in the interlobular spaces. Although the typical lesion of hepatic venous congestion was present in 3 of the 11 cases, it cannot be regarded as the origin, because venous congestion was completely absent in the remaining 8 cases. The venous congestion was unquestionably the consequence of the superimposed myocardial failure which these 3 patients revealed in their clinical story. Nevertheless, one could not escape the concept that if the origin of the cirrhosis was not primarily cardiac it must at least be circulatory, and it remained to determine what disturbing element in the circulatory dynamics of diffuse toxic goiter might account for the lesion. Inasmuch as the form of the cirrhosis which I have described is apparently pathognomonic of diffuse toxic goiter, it seemed reasonable to assume that some factor in the circulatory dynamics that is peculiar to this disease was responsible. This factor I believe is the increased velocity of the blood flow as measured by the circulation time. Anemia excepted, no other malady is associated with a consistently increased velocity of blood flow.

The increased velocity of blood flow in patients with diffuse toxic goiter was first demonstrated with the radium method by Blumgart, Gargill and Gilligan.²¹ Normally they found that the arm to heart

19. Moschcowitz, E.: Pathogenesis of Brown Induration of the Lung, *Am. Heart J.* 6:171, 1930.

20. Moschcowitz, E.: Phlebosclerosis of the Hepatic Veins, in *Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman*, New York, International Press, 1932, vol. 2, p. 857.

21. Blumgart, H. L.; Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow: The Circulatory Responses to Thyrotoxicosis, *J. Clin. Investigation* 9:69, 1930.

circulation time averaged 6.6 seconds, while the crude pulmonary circulation time (from the heart to the arteries about the elbow) averaged 10.8 seconds. In patients with diffuse toxic goiter the arm to heart circulation time averaged 4.9 seconds, while the crude circulation time averaged 5.9 seconds. These findings were confirmed by Tarr, Oppenheimer and Sager,²² employing the sodium dehydrocholate method, and by many others since. The finding of a rapid circulation time confirms a surmise afforded by clinical observation that in exophthalmic goiter the skin is flushed and warmer than normal, that there is a feeling of increased heat although the rectal temperature is within the normal range, that there is increased perspiration and that the pulse pressure is increased. All observers agree that in mass data there is a correlation between the velocity of the blood flow and the basal metabolic rate, although in an individual case this relation does not always hold. Moreover, the increased velocity of blood flow in patients with diffuse toxic goiter is inseparably linked with an increased blood volume,²³ an increased cardiac output²⁴ and an increased peripheral blood flow as measured by the formula cc./sq.M./min.²⁵ These factors in the circulatory dynamics of the disease are reversible after the administration of strong solution of iodine U. S. P. and especially after subtotal thyroidectomy. In myxedema the opposite relations are maintained.²⁵

The significance and the interrelationships of these disturbed circulatory functions and the compensatory adjustments have by no means been clarified. Such a discussion is reserved for a future communication on a planned study of the cardiodynamics of patients with diffuse toxic goiter. For the present, I am concerned only with their factual presence and their bearing on the pathogenesis of the cirrhosis which I have described. To elucidate my concept a knowledge of the circulation of the liver is essential.

22. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *Am. Heart J.* **8**:766, 1933.

23. (a) Liljestrand, G., and Stenström, N.: Blood Flow and Blood Pressure in Exophthalmic Goitre, *Acta med. Scandinav.* **63**:99, 1925. (b) Chang, H.: The Blood Volume in Hyperthyroidism, *J. Clin. Investigation* **10**:475, 1931. (c) Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow in Ten Women Exhibiting Graves' Disease, *J. Mt. Sinai Hosp.* **8**:1051, 1942. (d) Gibson, J. G., Jr., and Harris, A. W.: Clinical Studies of the Blood Volume: Hyperthyroidism and Myxedema, *J. Clin. Investigation* **18**:59, 1939.

24. Fullerton, C. W., and Harrop, G. A., Jr.: The Cardiac Output in Hyperthyroidism, *Bull. Johns Hopkins Hosp.* **46**:203, 1930. Boothby, W. M., and Rynearson, E. H.: Increase in Circulation Rate Produced by Exophthalmic Goitre, *Arch. Int. Med.* **55**:547 (April) 1935. Liljestrand and Stenström (23a).

25. Evans, W. F., and Stewart, H. J.: Peripheral Blood Flow in Myxedema, *Arch. Int. Med.* **69**:808 (May) 1942.

The Vascular Supply of the Liver.—Aside from the lung, the liver is the only organ that has both an arterial and a venous supply, but whereas the bronchial artery carries only a small fraction of the total blood to the lungs and supplies only the supporting tissues of that organ, the hepatic artery carries a much greater quantity of blood, estimated by Burton-Optiz²⁶ as approximately 25 per cent, by Barcroft and Shore²⁷ as 39 per cent, by MacLeod and Pearce²⁸ as 26 to 32 per cent and by Grab, Janssen and Rein²⁹ as between 12 and 22 per cent. Furthermore, the hepatic artery supplies not only the supporting structures but also, though to a lesser degree than the portal vein, the parenchyma. This is clearly manifest in an animal with an Eck fistula, in which the liver remains viable and even retains many of its functions, although to a lesser degree than is normal, for an appreciable period.³⁰ In this connection the observation of Barcroft and Shore²⁷ is pertinent. They found that the liver, in both fasting and fed animals, takes its dominating supply of oxygen from the hepatic artery. The hepatic artery is therefore of much greater physiologic significance than the bronchial.

While most observers are agreed on the manner of distribution of the portal blood supply of the hepatic lobule, controversy still centers on the precise mode of communication between the portal vein and the hepatic artery within the liver, and it is in the elucidation of this anatomic arrangement that, I believe, the pathogenesis of the cirrhosis occurring in the livers of patients with diffuse toxic goiter depends. That the portal vein and the hepatic artery communicate within the liver has been amply demonstrated not only by the Eck fistula but more directly by the observation that blood injected into the hepatic artery escapes from the portal vein and, but to a lesser degree, vice versa. Now, inasmuch as the pressure within the hepatic artery is practically that within the brachial, i. e., 130 mm. of mercury,³¹ and the pressure in the portal vein is low, estimated to be between 6 and 12 mm. of mercury,³¹ these pressures must be neutralized somewhere within the liver. The earlier authors accepted the theory of Gad,³² who postulated that the union

26. Burton-Optiz, I. R.: *The Vascularity of the Liver: I. The Flow of Blood in the Hepatic Artery*, *Quart. J. Exper. Physiol.* **3**:297, 1910.

27. Barcroft, J., and Shore, L. E.: *The Gaseous Metabolism of the Liver: I. In Fasting and Late Digestion*, *J. Physiol.* **45**:296, 1912-1913.

28. MacLeod, J. J. R., and Pearce, R. G.: *The Outflow of Blood from the Liver as Affected by Variations in the Condition of the Portal Vein and Hepatic Artery*, *Am. J. Physiol.* **25**:87, 1914.

29. Grab, W.; Janssen, S., and Rein, H.: *Ueber die Grösse der Leberdurchblutung*, *Ztschr. f. Biol.* **89**:324, 1929.

30. Whipple, G. H., and Hooper, C. W.: *Bile Pigment Output Influenced by the Eck Fistula*, *Am. J. Physiol.* **42**:544, 1917.

31. MacLeod, J. J. R.: *MacLeod's Physiology in Modern Medicine*, ed 9, St. Louis, C. V. Mosby Company, 1941, p. 503.

between the arterial capillaries and the portal channels occurs at an acute angle, forming at these points a wedge-shaped valve which shifts as the pressure bears on the sides of the flap. With normal pressure the valve permits an even flow from the arterial to the venous channels. When pressure is increased in the portal vein, flow and pressure are reduced in the hepatic artery, and vice versa. All later observers have abandoned this hypothesis because it ignored the capillary network that has since been amply demonstrated between the two vessels.

While the distribution of the blood from the portal vein to the sinusoids of the liver has been well clarified, the demonstration of the terminal ramifications of the hepatic artery has been the subject of much dispute. It has long been accepted since the pioneer work of Kiernan,³³ and repeatedly confirmed, that the hepatic artery terminates, within the capsule of Glisson, in capillaries of slender caliber which supply the walls of the bile ducts, the larger branches of the portal vein (*vasa vasorum*) and the connective tissue structure of the capsule itself. For a long time this was regarded as the sole function of the hepatic artery, and even in comparatively modern times some observers still hold to this view. Inasmuch as it was known that the portal vein and the hepatic artery communicate, it was assumed that these capillaries eventually formed venules, the internal hepatic venules or *rami vasculosi venosi*, which then supplied the hepatic sinusoids, thus establishing a communication between the artery and the vein. More recent observations of Mall,³⁴ Olds and Stafford,³⁵ Fiessinger and Walter³⁶ and Aunap³⁷ have shown that these venules do not exist. Observers are agreed that there is no communication between the capillaries of the hepatic artery and the portal vein within the capsule of Glisson proper. The communication must therefore occur outside the capsule.

Experiments in which a visualizing material was injected directly into the hepatic artery have shown that this vessel terminates in a capillary network that supplies the walls of the bile ducts and the portal vein within the capsule of Glisson. But the periphery of the hepatic lobule is also filled. This is accomplished in large part by a narrow

32. Gad, J.: Studien über Beziehungen des Blutstroms in der Pfortader zum Blutstrom in der Leberarterie, Inaug. Dissert., Berlin, G. Schade, 1873.

33. Kiernan, F.: The Anatomy and Physiology of the Liver, Phil. Tr., London **123**:711, 1833.

34. Mall, F. P.: A Study of the Structural Unit of the Liver, Am. J. Anat. **5**:227, 1906.

35. Olds, J. M., and Stafford, E. S.: On the Manner of Anastomosis of the Hepatic and Portal Circulations, Bull. Johns Hopkins Hosp. **47**:176, 1930.

36. Fiessinger, N., and Walter, H.: L'exploration fonctionnelle du foie et l'insuffisance hépatique, Paris, Masson & Cie, 1925.

37. Aunap, E.: Ueber der Verlauf der Arteria hepatica in der Leber, Ztschr. f. mikr.-anat. Forsch. **25**:238, 1931.

arteriole³⁸ that courses in the vascular septums, whence it breaks into capillaries that supply the adjacent sinusoids. To a much lesser degree some of the capillaries that supply the large bile ducts communicate directly with the peripheral sinusoids of the hepatic lobule. These

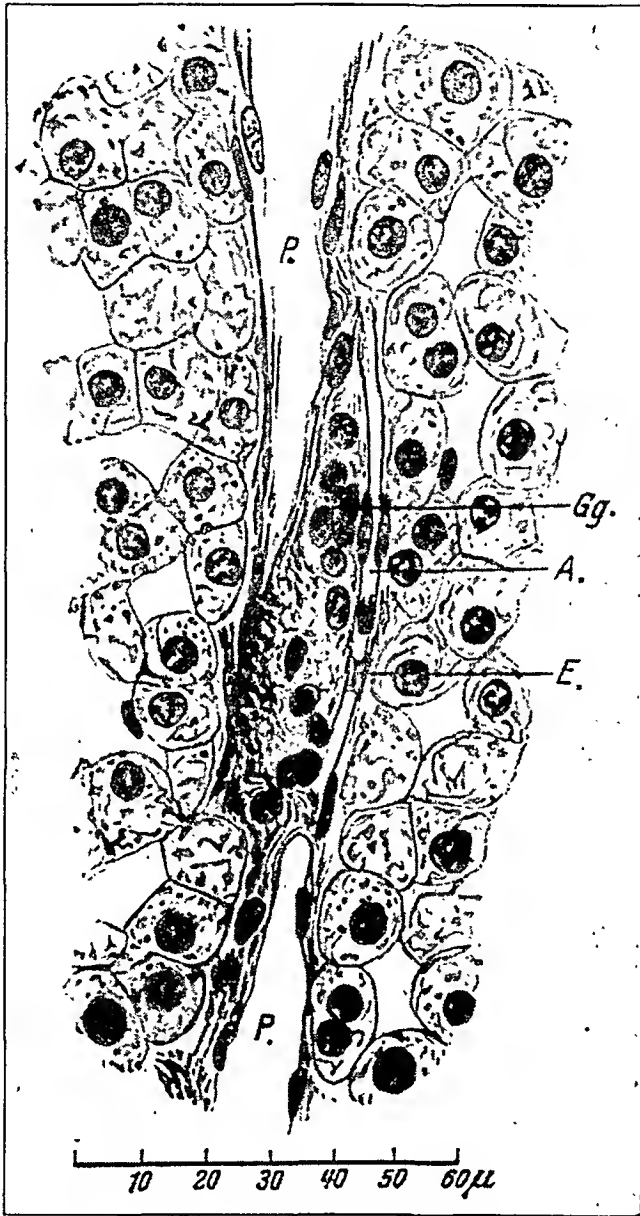


Fig. 11.—High power illustration of a normal vascular septum: *P.*, portal venule; *A.*, arteriole; *Gg.*, bile duct; *E.*, a longitudinally compressed erythrocyte. (The illustration is taken from Pfuhl.¹⁷)

38. Gilbert, A., and Villaret, M.: Contribution à l'étude de la circulation du lobule hépatique, *Compt. rend. Soc. de biol.* 67:521, 1909. Geraudel, E.: La double circulation capillaire de la glande hépatique, *ibid.* 58:818, 1905. Mall.³⁴

arterioles are always accompanied by a small branching portal venule and by a tiny bile duct (fig. 11). These three structures penetrate between the individual lobules, and the vascular channels break up and communicate between the nodal points by a fine capillary network that surrounds each lobule (fig. 12). In the pig these interlobular structures are particularly prominent. These vessels have been termed *vasa interlobularia* by Kiernan³³ and *rami vasculares septales* by Pfuhl.¹⁷ Olds and Stafford³⁵ have shown by serial sections that these arterioles represent the so-called translobular arteries described by Braus.³⁹ According to Pfuhl,¹⁷ these arterioles are very slender, averaging 8 microns in diameter, and consist of an endothelial lining and

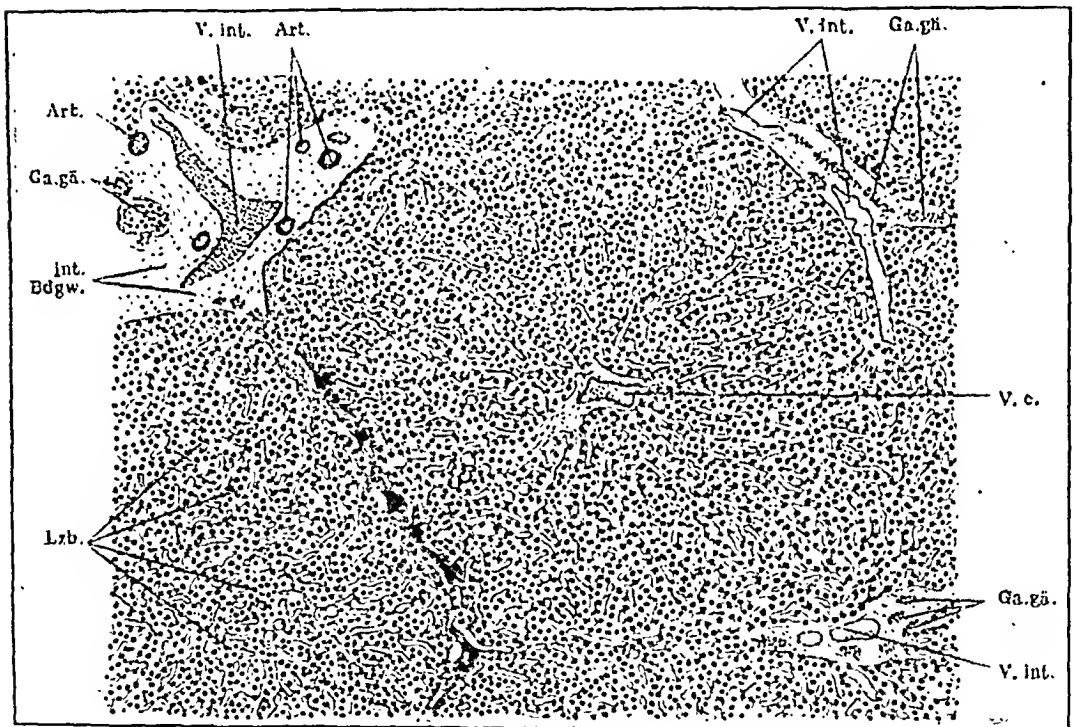


Fig. 12.—Diagrammatic representation of a normal hepatic lobule: *Art.*, arterial branches; *Ga. gā.*, bile ducts; *int.*, interlobular connective tissue; *Lzb.*, hepatic trabeculae; *V. c.*, central vein; *V. int.*, interlobular vein. (The illustration is taken from Sobotka, J.: *Textbook of Human Histology and Microscopic Anatomy*, New York, G. E. Stechert & Company, 1930, vol. 2.)

a sparse adventitia containing cells which, he believes, possess contractile powers (fig. 13). However, in studying many sections of normal livers I have noted that occasionally the walls contain muscle bundles, both longitudinal and transverse. It is noteworthy, for the interpretation of the peculiar localization of the cirrhosis of diffuse toxic goiter, that these interlobular arterioles arise only in the smaller division of the capsule of Glisson—according to Mall, “throughout the extent of the

39. Braus, H.: *Anatomie des Menschen*, Berlin, Julius Springer, 1924.

vessels of the sixth and possibly of the fifth order" (fig. 14). Quoting Olds and Stafford,³⁵

... the hepatic arterial capillaries do not anastomose directly with the portal vein radicles within the portal spaces. Instead, the arterial capillaries enter the hepatic sinusoids independently of the venous anastomoses. Slender capillaries arise either as the ultimate radicles of fine branches of the hepatic artery, or as

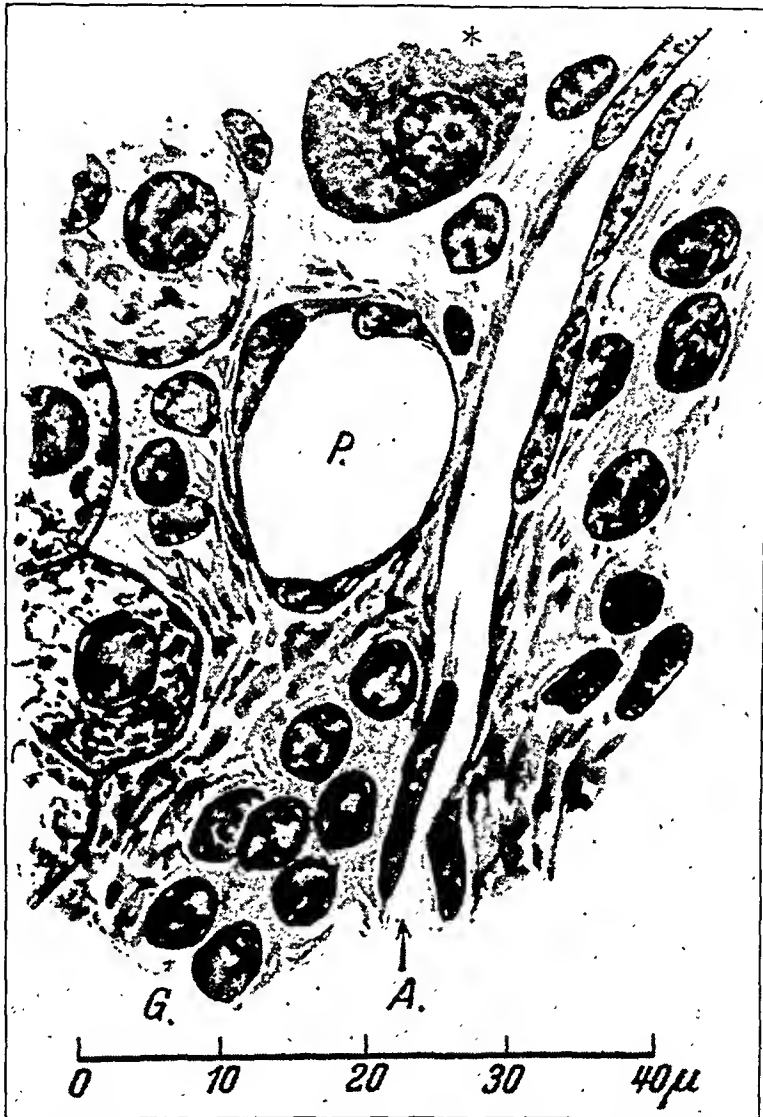


Fig. 13.—Vascular septum of normal human liver; G., septal bile duct; A., artery; P., branch of portal vein. (This illustration is taken from Pfuhl.¹⁷)

offshoots from the capillary plexuses surrounding the bile ducts. These capillary branches course towards the periphery of the portal space and anastomose with the hepatic sinusoids. The junctions of the arterial capillaries with the sinusoids are always independent of, and at some distance from, the similar communications established by the veins. Hence the most peripheral sinusoids are initially either distinctly arterial or venous, as the case may be. The venous connections are more

numerous, approximately four to five venules communicating with the sinusoids of a lobule to one arterial connection.

The portal venous capillary network is therefore correspondingly more extensive than the hepatic arterial network and contributes the first and a significant factor in equalizing the difference in pressures between the hepatic artery and the portal vein within the hepatic parenchyma by lowering the peripheral resistance. There is a second anatomic factor that helps in the equalization of pressures. Mall,³⁴ Aunap³⁷ and Olds and Stafford³⁵ have shown that the average diameter of the terminal hepatic arterioles is only 8 microns, whereas the average diameter of the hepatic sinusoids is 9 microns, so that at the point of

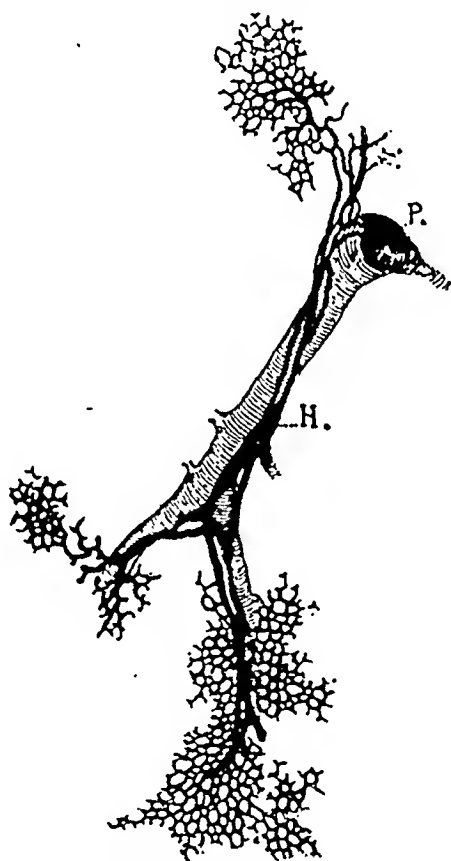


Fig. 14.—Diagrammatic representation of the smallest divisions of a portal space, showing the termination of the hepatic artery: *P.*, portal vein; *H.*, hepatic artery. The portal vein was first plugged with a granular mass and then an aqueous solution of prussian blue was injected into the artery. The extent of the capillary injection of the blue is shown. (This illustration is taken from Mall.³⁴)

communication with the sinusoids there is a sudden abrupt widening (fig. 15). This observation was confirmed by Wakim and Mann⁴⁰ when they directly observed blood flow in living amphibian and mammalian livers by the technic of quartz-rod illumination. Although this difference in caliber appears small, the effect on the blood flow is con-

40. Wakim, K. G., and Mann, F. C.: The Intrahepatic Circulation of the Blood, *Anat. Rec.* 82:233, 1942.

siderable when the difference in diameter is multiplied by the large number of such arterioles within the organ. A third factor in the equalization of pressures arises from anastomotic communications between the corresponding ramifications of the portal vein and the hepatic artery in their interlobular course. These have been demonstrated by Wakim and Mann in both amphibian and mammalian livers,

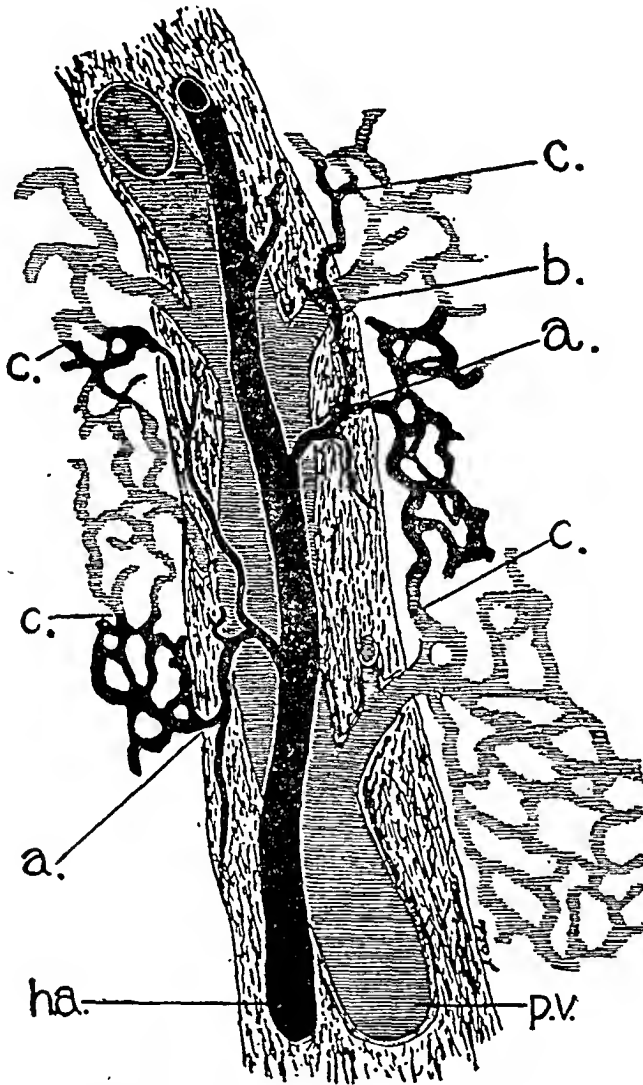


Fig. 15.—A longitudinal section through an interlobular or portal space. Note the distribution of the hepatic arterioles (*a.*), portal venules (*b.*) and the inter-sinusoidal communications (*c.*). The abrupt transition from narrow arterial channel to wide sinusoidal channel is illustrated. Note the mixing of the two injection masses at the level of the first sinusoidal anastomosis and thereafter. (This illustration is taken from Olds and Stafford.³⁵)

though not so frequently in the latter as in the former (fig. 16). These observers also noted that arterial ramifications end in the terminal branches of the portal vein before the latter empty into the sinusoids at the peripheries of the lobules.

Synthesis.—The equalization of pressure between the hepatic artery and the portal vein within the liver is accomplished in greater part at least by an intercommunicating capillary network whereby blood flows from a small basin to one four or five times as great, from a conducting system of narrow vascular channels to those of slightly larger diameter, and finally by arteriovenous communications interposed between the terminal ramifications of the two vessels. The peripheries of the hepatic lobules are therefore supplied by either arterial or venous blood and

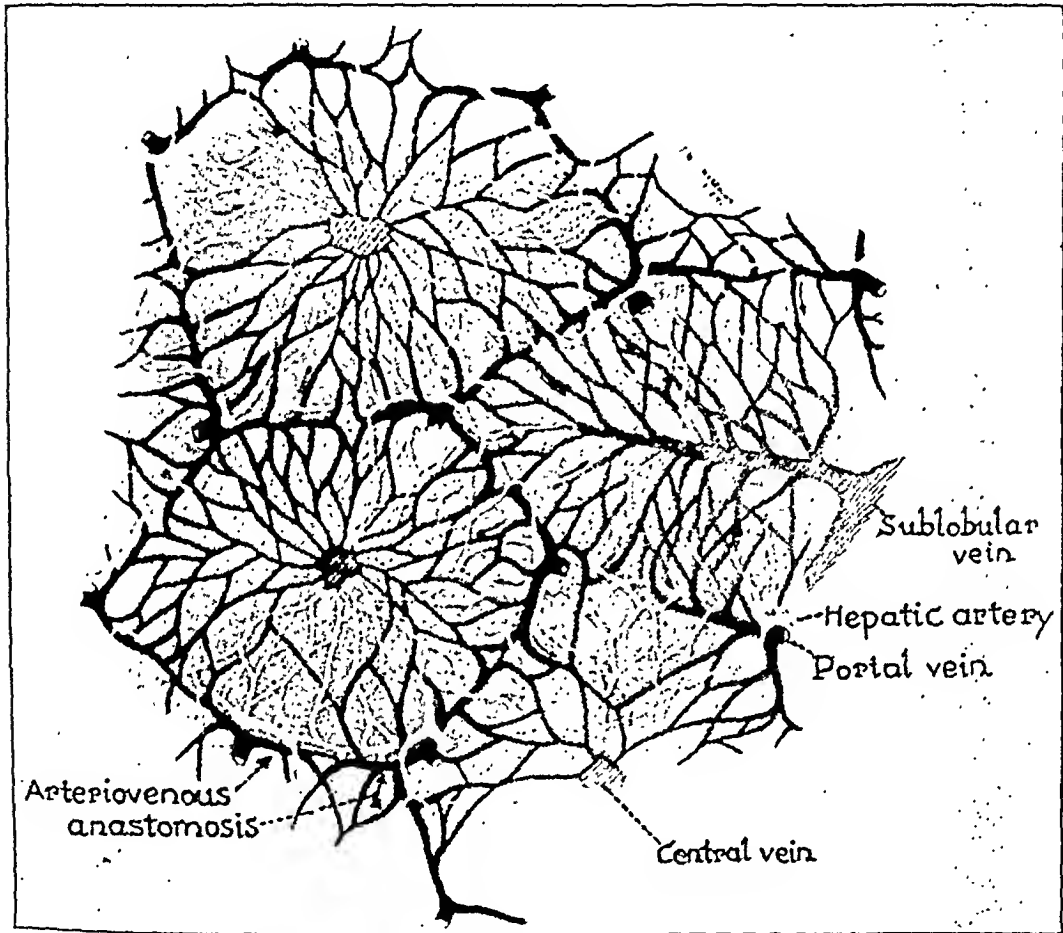


Fig. 16.—Diagrammatic representation of the communication of the arterial and the venous blood within the mammalian liver. White identifies the arterial, black the portal and shading the hepatic venous radicles. Anastomoses between the arterial and the portal radicles as they course through the interlobular spaces are noted here. (The illustration is taken from Wakim and Mann.⁴⁰)

only to a much lesser extent by an admixture of both bloods. It is only in the deeper sinusoids of the liver that all the arterial and the venous blood eventually meet (fig. 17).

My description refers entirely to static conditions. The vascular supply of the liver is profoundly influenced by vasomotor reactions, and this affects the function of the liver in providing a blood depot, in regulating the supply of blood to the right side of the heart and in inte-

grating these vasomotor responses with those in other systemic vessels.⁴¹ How these reactions are affected in patients with diffuse toxic goiter is not known.

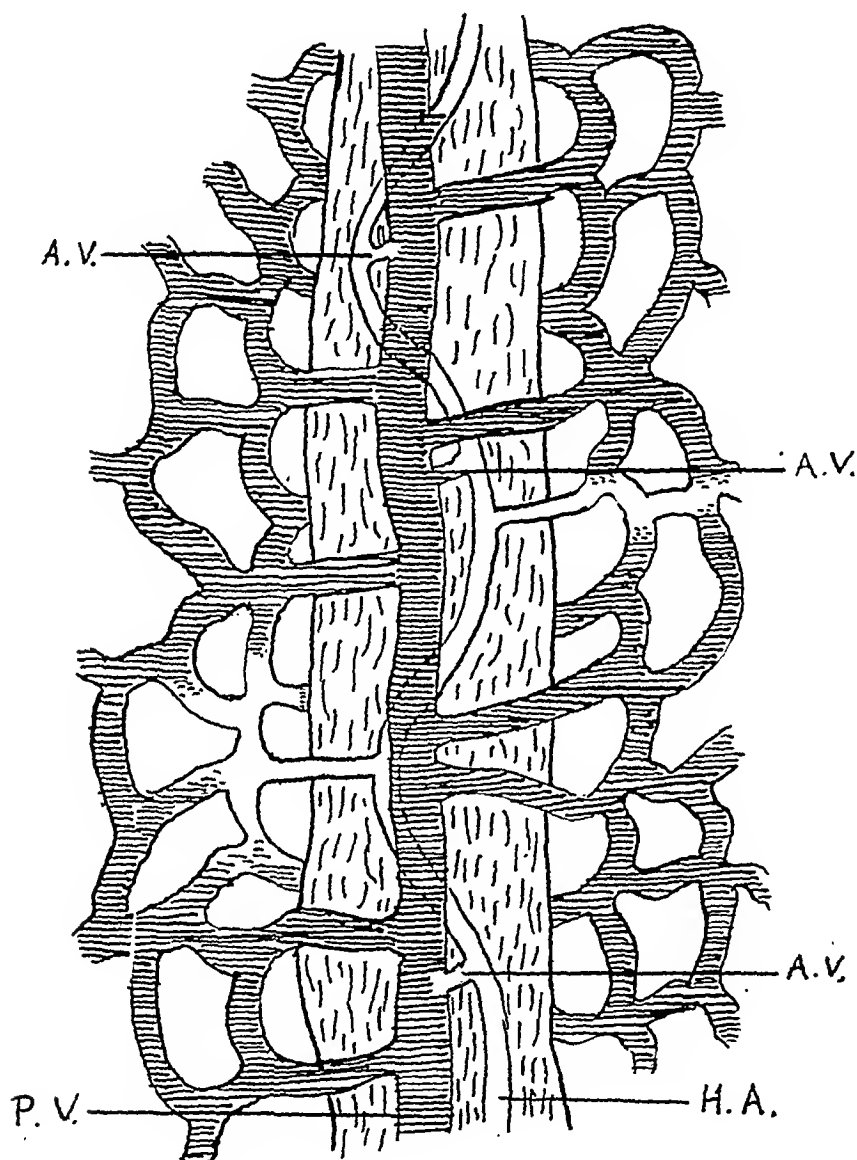


Fig. 17.—Diagrammatic representation of a vascular septum showing the different mechanisms whereby the intravascular pressures are equalized between the hepatic artery and the portal vein. Note (1) the communications between the terminal capillaries of the hepatic artery and the terminal capillaries of the portal vein in the border zones of the adjacent lobules and the sudden widening of arterial capillaries into venous; (2) the larger number of the portal branches as compared with the arterial; (3) the arteriovenous anastomoses within the vascular septum. The bile duct has been omitted, for purposes of clarification. (The illustration is a modification from Olds and Stafford.³⁵) *H.A.* indicates the hepatic artery *P.V.* the portal vein; *A.V.* the arteriovenous anastomoses.

41. Katz, L. N., and Rodbard, S.: The Integration of the Vasomotor Responses in the Liver with Those in Other Systemic Vessels, *J. Pharmacol. & Exper. Therap.* 67:407, 1939.

These anatomic considerations in association with the altered circulatory dynamics in patients with diffuse toxic goiter lead to the following interpretation of the pathogenesis of this peculiar type of hepatic cirrhosis.

It should be recalled that, as best determined in the early phases of the lesion, the areas of cirrhosis are wedge shaped and, when confluent, stellate, and are situated between the lobules; also, that in serial sections the narrow portion of the wedge can be traced to the splitting up of a branch of the hepatic artery that arises from the Glisson capsule and penetrates in the vascular septums, when it proceeds directly either through the peripheral portions of two adjacent lobules or through an entire lobule and terminates in a central vein or in a collecting vein arising from the conglomeration of a number of central veins. It is therefore at the site where the interlobular hepatic artery supplies the periphery of the hepatic lobule—the predominant location of intrahepatic equalization of the pressures between the hepatic artery and the portal vein—that the cirrhotic process arises. This observation is consistent with the fact that such cirrhotic areas are visible only in the neighborhood of the smaller divisions of the capsules of Glisson, from which these narrow hepatic arterioles exclusively arise. Furthermore, it should be recalled that with higher magnifications the early manifestations of the cirrhotic process are represented by pronounced capillary dilatations, with corresponding trabecular atrophy, which eventually parallel the finer morphologic characteristics of a congestive liver. To account for this I now invoke the clinical observation, particularly peculiar to diffuse toxic goiter, that there is increased velocity of blood flow and that this is associated with increased blood volume and increased arterial blood flow. While compensatory adjustments to the increased velocity of blood flow undoubtedly occur in the early phases of this disease, eventually this disturbance of circulatory dynamics must take its toll, so that the blood which enters the terminal ramifications of the hepatic artery no longer can be carried away as fast as it enters. The intrahepatic equalization of pressure between the hepatic artery and the portal vein is no longer maintained; stasis must ensue, resulting in dilatation of the neighboring capillaries. In time this is projected deeper into the parenchyma until the dilated capillaries pour their blood into the central or the collecting veins. The time factor is obviously of importance, which explains why the cirrhosis is observed usually in the later phases of the disease. In this respect it is precisely comparable to cardiac cirrhosis. In other words, the morphologic beginnings and subsequent progression of this lesion are precisely what I have tried to demonstrate as capillary sclerosis in cardiac cirrhosis arising in congestive failure,^{28d} the difference being that in cardiac cirrhosis there is backward failure, while in the cirrhosis of diffuse toxic goiter the failure

occurs in a forward direction. Topographically the lesions of the two types of cirrhosis are different; in cardiac cirrhosis the lesion begins around the central vein; in the cirrhosis of diffuse toxic goiter, it is at the periphery of the lobule. In diffuse toxic goiter, if chronic congestion is superimposed, both sites are involved. Parenthetically, the increased velocity of blood influences the circulatory dynamics in other respects. This is suggested by the clinical observation that in about a third of patients with diffuse toxic goiter the pulmonary conus is enlarged.⁴² Curiously, Saltykow⁴³ reported a peculiar type of congested liver that differed from the conventional nutmeg type in that the congestion was not around the central vein but was between the branches of the periportal connective tissue, in the form of projections which eventually became star shaped and might even encircle a lobule or lobules. This description resembles closely that of the cirrhosis of diffuse toxic goiter. Regrettably Saltykow gives no clinical correlations.

My interpretation of the pathogenesis necessitates an explanation of the noteworthy subcapsular predilection of the lesion. This predilection is not peculiar to this form of cirrhosis, and it is interesting that it is usual in the livers of patients with congestive failure.⁴⁴ Inasmuch as there is not the slightest evidence that there is a difference of vascularity in these areas, local conditions must be ascribed as the cause. I feel strongly that the peripheral resistance engendered by the firm capsule of the liver is the main if not the only factor. This was suggested by Fahr^{44b} as the cause of the subcapsular prominence of the lesions of the congested liver, and there are a number of reasons for assuming similar mechanisms for the cirrhosis of diffuse toxic goiter. First, as was shown in a previous study,⁴⁵ one of the important factors in the localization of arteriosclerosis and phlebosclerosis is the degree of external resistance surrounding the involved vessel—for instance, the prominence of patches of sclerosis of the aorta at the site of the intervertebral disks as compared with the hollows between⁴⁶; the greater incidence of patches of sclerosis of the pulmonary artery where the vessels lie against the firm rings of the bronchi⁴⁵; the predilection of

42. Parkinson, J., and Cookson, H.: *The Size and Shape of the Heart in Goitre*, Quart. J. Med. **24**:499, 1931.

43. Saltykow, S.: *Ueber Stauungsleber*, Verhandl. d. deutsch. path. Gesellsch. **5**:104, 1902.

44. (a) Gerlach, W., in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1930, vol. 5, p. 90. (b) Fahr, T.: *Zur Frage der chronischen Stauungsleber*, Zentralbl. f. Herzkrankh. **4**:368, 1912.

45. Moschcowitz, E.: *Vascular Sclerosis*, New York, Oxford University Press, 1942.

46. Westenhoeffer: *Ueber die Lokalisation und phylogenetische Grundlage der Aorta und ihrer Aeste*, Deutsche med. Wchnschr. **48**:518, 1922.

patches of sclerosis for those areas of arteries that lie against bone (this is seen in the arteries of the calvarium⁴⁷ and in the radial artery⁴⁸); finally, the Cramer and Schilling⁴⁹ area of sclerosis in the lower end of the inferior vena cava which lies against the rigid aorta and where the two currents of the common iliac veins meet. Now, the incidence of capillary sclerosis parallels that of vascular sclerosis; this is exemplified in the glomeruli and the islands of Langerhans in hypertension of the greater circulation, in the walls of the pulmonary alveoli in hypertension of the pulmonary circuit and around the hepatic central veins in sclerosis of the hepatic vein in long-standing congestive failure,⁴⁵ so that sclerosis of the larger vessels and capillary sclerosis are usually simultaneous lesions. That external resistance is a factor in the production of capillary sclerosis is additionally exemplified by my observation that the most prominent lesions are witnessed in the peripheral portions of the lung where the capillaries are adjacent to the pleural surface and that sclerosis of the hepatic parenchyma occurs immediately adjacent to a greatly dilated hepatic vein (fig. 18).

Finally, the factor of external capsular resistance is well exemplified in a liver from a person who died of cardiac failure in the course of diffuse toxic goiter. On the surface of the liver were two deep grooves, the result of pressure from two abnormally situated ribs. Although the organ did not reveal the characteristic cirrhosis of diffuse toxic goiter, but only evidences of marked chronic congestion, there was in the subcapsular areas a considerable increase of connective tissue, which extended a short distance into the parenchyma and was limited exclusively to the grooves (fig. 19). The lesion resembled that found in the late phases of cardiac cirrhosis.

One may well inquire why the cirrhosis of diffuse toxic goiter is sometimes absent in cases in which the history of the disease is apparently one of long duration. In 3 of my cases without cirrhosis the duration of the disease was given as one year or more. It is interesting to note that in all 3 chronic venous congestion was shown at autopsy; in 2 there was associated disease of the coronary arteries. It is probable that the circulatory dynamics were modified by the incidence of venous congestion. Blumgart, Gargill and Gilligan²¹ and Tarr, Oppenheimer and Sager²² have shown that the onset of congestive failure prolongs the circulation time to normal limits. According to Tarr and

47. Lauda, E.: Physiologische Druckschädigungen und Arteriosklerose der Duralgefäße, *Beitr. z. path. Anat. u. z. allg. Path.* **58**:180, 1921.

48. Dow, D. R.: The Incidence of Arteriosclerosis in the Vessels of the Body, *Brit. M. J.* **2**:162, 1925.

49. Cramer, H.: Beiträge zur Atherosklerosefrage, *Virchows Arch. f. path. Anat.* **230**:46, 1921. Schilling, W.: Ueber Phlebosklerose, ihre Entstehungsweise und Ursachen, *ibid.* **262**:658, 1926.

co-workers, the circulation time in patients with congestive failure and diffuse toxic goiter seems to be an arithmetical average of what would be expected in either condition alone. It is certain that congestive failure may arise in patients with diffuse toxic goiter before cirrhosis occurs; this is proved by the finding of a congested liver without cirrhosis in 10 of my series. In 2 of the 3 cases of long duration the congestive failure was probably induced by an associated disease of the coronary vessels.



Fig. 18.—Area of marked fibrosis surrounding a greatly dilated large branch of a sclerotic hepatic vein (O) of a patient with marked congestive failure.

HEPATIC CHANGES IN EXPERIMENTAL HYPERTHYROIDISM

It was natural to infer that this type of cirrhosis might be reproduced experimentally by administration of thyroid. Attempts to do this have been fully summarized by Lichtman.⁵⁰ The findings aside from depletion of glycogen have been inconsistent. Some observers have reported fatty or parenchymatous degeneration; others have reported increases

50. Lichtman, S. S.: *Diseases of the Liver*, Philadelphia, Lea & Febiger, 1942, p. 621.

of weight despite the depletion of glycogen. Some have reported foci of necrosis after thyroid feeding; others have not. When foci of necrosis were found, there was always an associated infection, so that it is impossible to say whether the necrosis was caused by the thyroid feeding or by the infection or by a combination of both. No one has even remotely reproduced the type of cirrhosis I have discussed, and this might have been expected for the reason that genuine diffuse toxic goiter has not been successfully reproduced experimentally. At most only part of the



Fig. 19.—An area of marked fibrosis limited exclusively to the subcapsular area and caused by pressure of a rib in a person with congestive failure.

picture has been reproduced, namely, the hyperthyroid element. As I pointed out in a previous communication,¹⁵ exophthalmic goiter represents hyperthyroidism plus a number of other features. This is why I do not regard hyperthyroidism and exophthalmic goiter, or diffuse toxic goiter, as synonymous terms.

SUMMARY

A type of hepatic cirrhosis apparently pathognomonic of diffuse toxic goiter was found in 10 of 31 cases. The lesion is identical in both

form and progression with that seen in chronic hepatic venous congestion and cardiac cirrhosis but differs from the latter in that topographically it is not around the central veins but in the interlobular septums, often encroaching on the lobule itself. In the early phases the areas of fibrosis can be traced to the terminal ramifications of the hepatic artery as it passes into the interlobular vascular septums. This artery and its ramifications represent a significant factor of the equalization of intravascular pressures between the hepatic artery and the portal vein within the liver.

Pathogenetically, I believe, the lesion is the consequence of the increased velocity of blood flow, an invariable accompaniment of, and almost peculiar to, this disease in the early phases. The increased velocity is associated with increased blood volume and increased blood flow. These altered circulatory dynamics render the maintenance of the normal pressure relations between the hepatic artery and the portal vein difficult; eventually decompensation arises, with resulting stasis in these areas, and the lesion begins as capillary congestion. In time, just as in chronic venous congestion of central origin, capillary sclerosis results, with eventual fibrosis. In this conception, the cirrhosis of diffuse toxic goiter is the consequence of forward failure, while that of chronic hepatic venous congestion is the result of backward failure. The cirrhosis is distinguished by the fact that it is predominantly in the subcapsular zone of the liver. Evidence is submitted that, as in the ordinary congestive liver, this is due to the resistance offered by the capsule of the liver. The cirrhosis also possesses the peculiarity that it arises only from the smaller subdivisions of the portal spaces. This is because the interlobular branches of the hepatic artery arise only from such spaces. The cirrhosis bears a definite but not absolute relation to the duration of the malady, which is what one might expect from the pathogenesis. Nevertheless, this cirrhosis is sometimes absent in persons who submit a history of apparent long duration of the disease. This may be accounted for by the observation that chronic venous congestion is an exceedingly common sequence of long-standing diffuse toxic goiter, even in patients without cirrhosis, and that this venous congestion neutralizes the increased velocity of blood flow.

CANICOLA FEVER

Case Report and Review of the Literature

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CANICOLA fever, or leptospirosis canicola, is a rare disease. Although there is an abundance of literature on Weil's disease, or leptospirosis icterohaemorrhagica, there is a paucity of written material on canicola fever. Consequently it was felt advisable to present this case which was seen by the author and to review the literature on the subject.

REPORT OF A CASE

A 44 year old captain of Italian extraction entered Fitzsimons General Hospital on Oct. 1, 1945, giving a history of having suffered a sudden onset of sharp pain across the bridge of his nose with associated nasal congestion during the evening six days previous to admission. Within an hour after the onset of his difficulties the patient had a headache and pains in his hips. He also felt feverish and was sweaty. He took to his bed and remained there for the succeeding four days with little change in symptoms. Since the patient was in San Antonio at the time on an emergency leave that had almost expired, he began driving toward Denver on the fifth day of his illness. During this day the patient noted that his eyes were bloodshot, and on the night of the fifth day he suffered severely from generalized arthralgia, myalgia, anorexia, malaise and nasal congestion. He continued driving on the sixth day of his illness; however, the muscle pains and malaise continued.

Physical examination on admission revealed the patient to be considerably jaundiced and acutely ill. His temperature taken orally was 103 F. His liver was felt 1 fingerbreadth below the right costal margin on deep inspiration and was slightly tender. The spleen was not palpable, and there was no lymphadenopathy. There was marked bilateral conjunctival injection. No costo-vertebral tenderness was present, nor was there evidence by physical examination of pneumonia or meningitis. Examination otherwise revealed nothing except for evidence of hypertrophic arthritis from which the patient had suffered for a few years.

Laboratory studies at the time of the patient's admission revealed a white blood cell count of 22,900, with 88 per cent polymorphonuclear cells. The red cell count was 4,250,000. The icteric index was 94; the corrected sedimentation rate was 26 mm. per hour; the cephalin-cholesterol reading was 2 plus, and the nonprotein nitrogen was 35 mg. per hundred cubic centimeters. The urine was normal except for the presence of bile, and the stools were light in color.

On admission the patient was started on a low fat, high carbohydrate, high protein diet with supplementary vitamins. He was rather anorexic during his first few hospital days and complained bitterly of generalized pains in joints and muscles and nasal congestion. On the third hospital day a roentgenogram of the

From the Medical Service, Fitzsimons General Hospital, Denver, Colo.

chest revealed bronchopneumonia at the right cardiophrenic angle. Administration of sulfadiazine was started, but due to lack of therapeutic response it was supplanted by penicillin on the sixth hospital day. This also failed to relieve significantly the patient's symptoms and was discontinued on the twelfth hospital day; however, the pulmonary infiltration had disappeared four days previously. By the tenth hospital day the patient's jaundice was much improved (the icteric index was 29.), although his myalgia and arthralgia persisted and was associated with a daily temperature between 100 and 102 F. orally. The conjunctival injection did not improve and caused the patient a great deal of discomfort. His white blood cell count had fallen to 12,000, with 60 per cent polymorphonuclear cells by this time. Shortly after the tenth hospital day the patient began to make a slow but steady improvement. His fever, arthralgia and myalgia were completely gone by the twenty-fifth hospital day, but his conjunctival injection proved obstinate and continued for his first thirty-five hospital days. The nature of this was unclear. Definite thickening of the bulbar conjunctiva developed, and three small nodules appeared on the right bulbar conjunctiva. All of this eventually cleared.

Agglutinations to *Leptospira icterohaemorrhagiae* were tried on the thirteenth hospital day with doubtful results. The patient was then questioned as to whether his dog had been ill, and it was learned that the patient's dog had been suffering from a severe, albeit ill defined, illness for the preceding two months. It was also learned that the patient was extremely fond of his dog and was in the habit of fondling the dog a great deal. Consequently the dog was obtained and samples of urine and blood were taken. Samples of serum from both the patient (taken on the twenty-fifth hospital day) and his dog were sent to the National Institute of Health; where it was discovered that both the serums agglutinated *Leptospira canicola* to a dilution of 1:100,000 and *L. icterohaemorrhagiae* to 1:1,000. *Leptospiras* were never seen in the patient's blood by dark field examination; however, they were found repeatedly in the patient's urine between the sixteenth and the twenty-ninth hospital day. Unfortunately the leptospiras were never isolated. No leptospiras were found in the dog's urine, but this may have been due to over-vigorous alkalization.

The patient was sent on a thirty-day convalescent leave on his forty-seventh hospital day. At this time he was asymptomatic. His corrected sedimentation rate was 12 mm. per hour; the cephalin-cholesterol reading was 2 plus, and the icterus index 13. His white blood cell count, serum proteins, alkaline phosphatase, hippuric acid excretion and nonprotein nitrogen were normal. The last four of these were never abnormal during his disease. On his return from his leave all his laboratory studies for evidence of hepatic damage were negative. A mild anemia which developed during his disease had disappeared. He had been asymptomatic during his leave and was discharged from the hospital.

It is of interest that at no time did the patient show evidence of nephritis, meningitis or hemorrhagic tendencies other than the conjunctival injection. Lumbar puncture was not performed.

HISTORY AND INCIDENCE

L. canicola was first isolated by Klarenbeek and Schüffner¹ in 1931. The leptospiras were differentiated from *L. icterohaemorrhagiae*

1. Klarenbeek, A., and Schüffner, W.: Appearance in Holland of *Leptospira* Differing from Weil Strain, Nederl. tijdschr. v. geneesk. 77:4271-4272 (Sept. 16) 1933.

by serologic methods. Although Schüffner² mentioned that a case of human infection with *L. canicola* was seen by a Dr. Cleyndert, of Delft, in September 1933, the first cases of this disease in human beings to be fully reported were those of Roos, Walch-Sorgdrager and Schüffner³ in 1937. They reported 11 cases from Holland, which is still the largest group of cases assembled by a single group of observers. The first case of the disease in a human being in the United States was reported in 1938 by Meyer, Eddie and Stewart-Anderson⁴ from San Francisco. As far as I have discovered this is the thirty-first case to be reported from the entire world and the sixth case from the United States. Cases have been reported from Holland,⁵ Austria,⁶ Denmark⁷ and China,⁸ and from San Francisco,⁹ New Orleans¹⁰ and Washington, D. C.,¹¹ in the United States. Although the cases were not reported in detail it is mentioned in the literature that the disease has been seen in Berlin, Vienna and in three other instances¹² in the United States.

2. Schüffner, W.: Recent Work on Leptospirosis, Tr. Roy. Soc. Trop. Med. & Hyg. **28**:7-31 (May 17) 1934.

3. Roos, C. J.; Walch-Sorgdrager, B., and Schüffner, W. A. P.: Epidemic of *Leptospira Canicola* Infection in Human Subjects and Dogs, Nederl. tijdschr. v. geneesk. **81**:3324-3325 (July 10) 1937.

4. Meyer, K. F.; Eddie, B., and Stewart-Anderson, B.: Canine, Murine and Human Leptospirosis in California, Proc. Soc. Exper. Biol. & Med. **38**:17-19 (Feb.) 1938.

5. (a) Legras, A. M., and Wolters, D. H. F.: Ophthalmologic Complications in Case of Weil's Disease Typhus Canicola, Ophthalmologica **99**:469-470 (May) 1940. (b) Roos, Walch-Sorgdrager, and Schüffner.³

6. Tetzner, E.: Serologisch sichergestellter Fall von Weilscher Krankheit—Typ *Leptospira canicola*—beim Menschen unter dem Bilde einer Meningitis, Klin. Wchnschr. **17**:508-509 (April 2) 1938.

7. (a) Brammer, E.; Petersen, C. B., and Scheel-Thomsen, A.: Case of Leptospirosis Canicularis Related to Weil's Disease, with Review of Clinical Picture, Ugesk. f. læger **100**:419-423 (April 21) 1938. (b) Bukh, N.: Case of Leptospirosis Canicularis with Marked Nephropathy, *ibid.* **102**:1142-1145 (Oct. 31) 1940. (c) Bjørneboe, M.: Two Cases of Leptospirosis Canicularis with Serous Meningitis, *ibid.* **103**:1281-1286 (Oct. 2) 1941.

8. Snapper, I.; Chung, H. L.; Chu, I., and Chen, K. C.: Preliminary Observations on Human, Canine and Murine Leptospirosis in North China, Chinese M. J. **58**:408-426 (Oct.) 1940.

9. (a) Meyer, K. F.; Stewart-Anderson, B., and Eddie, B.: "Canicola Fever," a Professional Hazard, J. Am. Vet. M. A. **93**:332 (Nov.) 1938. (b) Meyer, Eddie and Stewart-Anderson.⁴

10. Bruno, F. E.; Wilen, C. J. W., and Snavely, J. R.: Spirochetal Jaundice: Report on Fifteen Cases, Including Two Cases of *Leptospira Canicola* Infection, J. A. M. A. **123**:519-524 (Oct. 30) 1943.

11. Tievsky, G., and Schaefer, B. G.: Canicola Fever (*Leptospirosis Canicola*): Report of Human Case and Review of Literature, M. Ann. District of Columbia **13**:11-16 (Jan.) 1944.

Undoubtedly not all the cases that have been seen have been reported, and it is possible that a few cases were missed in the survey of the literature. Also, one may be sure that the disease has gone undiagnosed in an unknown number of cases. There undoubtedly have been sub-clinical infections when the person has not been aware of the fact that he was infected and did not consult a physician. At present it is impossible to estimate how frequently this may have occurred. Certainly one can expect more cases to be found when the medical profession is more acutely aware of the presence of this disease, and when it consequently looks for it more frequently. Such was the case with Weil's disease. At any rate canicola fever is a rare disease, and its presence is not fully appreciated by the medical profession at large.

At first it was thought that *L. canicola* was only a variant of *L. icterohaemorrhagiae* by some observers.¹³ At present, however, it is generally agreed that infection with *L. canicola* represents a distinct disease in that it varies from Weil's disease immunologically, in mortality, in its virulence on test animals and, perhaps, in some clinical aspects.

CLINICAL PICTURE

Unfortunately in many of the reports the clinical features presented by the cases are only summarized. Detailed data of the clinical features presented by each particular case are available in about a dozen instances. The number of cases reported is still much too small to offer more than generalities to one trying to define the clinical characteristics of this disease. At the beginning, however, it can be said that the clinical picture of this disease is strikingly similar to that seen in Weil's disease. As a matter of fact the diseases cannot be differentiated clinically. Generally speaking canicola fever tends to be milder than the illness caused by *L. icterohaemorrhagiae*.

The onset of the disease may be variable. In a large percentage of cases the onset has been sudden and stormy. Such onsets are marked by a high temperature (101 to 104 F.), pronounced malaise, chills, anorexia, myalgia and arthralgia. Abdominal distress seems to be somewhat less commonly seen than in Weil's disease. In other cases the onset is insidious. Meyer, Stewart-Anderson and Eddie^{9a} stated

12. (a) Randall, R., and Cooper, H. K.: Golden Hamster (*Cricetus Auratus*) as Test Animal for Diagnosis of Leptospirosis, *Science* **100**:133-134 (Aug. 11) 1944. (b) Larson, C. L.: Experimental Leptospirosis in Hamsters (*Cricetus Auratus*), *Pub. Health Rep.* **59**:522-527 (April 21) 1944. (c) Greene, M. R.: Survey for Leptospirosis in Southern California, *Am. J. Hyg., Sect. B* **34**:87-90 (Sept.) 1941.

13. Packchianian, A.: Prevalence of Infectious Jaundice in the United States as Determined by Agglutination and Animal Inoculation Tests, *Am. J. Path.* **14**: 638-642 (May 4) 1938.

that *L. canicola* infections can easily be mistaken for influenza, undulant fever or tuberculosis. The disease can be so mild that the patient never appreciates that he has been infected and consequently does not consult a physician.¹⁴ Roos and his associates³ reported such cases. Serologic evidence of the disease was found in mildly ill members of a family in which another member and the family dog had outspoken clinical evidence of the disease. The presenting symptoms of the disease may be neurologic, and cases have been reported¹⁵ when the only clinical evidence of disease was that of meningitis.

There are some clinical features seen often enough to warrant a brief discussion of each: 1. Jaundice: This classical sign, which is present in one half to two thirds of the cases of Weil's disease, was not seen in 12 cases of canicola fever reported from Holland.^{15a} Generally speaking this sign has been absent from the cases reported from Europe and China, but has been seen in half of the cases reported from the United States. This is interesting in that the same approximate variation has been seen in the canine *L. canicola* infections reported from the different continents. The variations in the symptom complex caused by *L. canicola* apparently reflect variations in virulence and individual properties of different strains of this organism. This variation from strain to strain is further emphasized by the fact that some strains of *L. canicola* readily kill hamsters,^{12a} while other strains are not so fatal.¹⁶ Meyer, Stewart-Anderson and Eddie¹⁷ stated that the pathogenicity of *L. canicola* does not parallel its icterogenic properties. 2. Nephritis: This complication of leptospiral infections is seen in canicola fever. All patients may show some mild albuminuria and cylindruria; however, this is not to be interpreted as evidence of nephritis. The Dutch investigators^{15a} found no remarkable urinary changes in their 12 cases. Since that time at least 3 instances¹⁸ of acute hemorrhagic nephritis have occurred. Azotemia occurred in 1 of the cases of Bruno, Wilen and Snavely.¹⁰ There is no evidence that chronic nephritis has resulted in human beings from this disease. 3. Meningitis: In 4 of 12 cases reported from Holland there were meningitic signs and symptoms. Walch-Sorgdrager,^{15a} in a comprehensive

14. Meyer, K. F.; Stewart-Anderson, B., and Eddie, B.: Epidemiology of Leptospirosis, *Am. J. Pub. Health* **29**:347-353 (April) 1939.

15. (a) Walch-Sorgdrager, B.: Leptospirosis, *Bull. Health Organ., League of Nations* **8**:143-386, 1939. (b) Roos, Walch-Sorgdrager and Schüffner.⁸ (c) Tetzner.⁶ (d) Bjørneboe.^{7c}

16. Morton, H. E.: Susceptibility of Syrian Hamsters to Leptospirosis, *Proc. Soc. Exper. Biol. & Med.* **49**: 566-568 (April) 1942.

17. Meyer, K. F.; Stewart-Anderson, B., and Eddie, B.: Canine Leptospirosis in United States, *J. Am. Vet. M. A.* **95**: 710-729 (Dec.) 1939.

18. Bukh.^{7b} Meyer, Stewart-Anderson and Eddie.^{9a} Bruno, Wilen and Snavely.¹⁰

study on leptospirosis, wrote in some detail of the meningitic form of leptospiral (either with *L. canicola* or *L. icterohaemorrhagiae*) infections. The only evidence of disease may lie in meningitic signs and symptoms. Evidence of meningitis occurred in both of Snapper's cases,⁸ and confusion, convulsions and delirium have been seen in other cases.

Some hemorrhagic tendency is present in almost all cases. Conjunctival injection is often present, and epistaxis is not rare. Pulmonary infiltrations are apparently somewhat less frequent than in Weil's disease.

Fever may vary considerably in type. It may be undulant, intermittent or sustained. Fever may be present for only a few days, or it may be present for weeks, even up to two months. Naturally, the duration of the disease is equally variable, and febrile relapses occur not infrequently, as is the case with Weil's disease. Cardiac involvement has been reported in only one instance,^{5a} this being transient partial heart block. Tievsky and Schaefer's¹¹ paper contains a chart of the clinical features of this disease.

As yet there have been no deaths from canicola fever, and only 1 instance of a complication⁸—a vitreous opacity in the left eye. Convalescence may be slow and weakness may be pronounced for a considerable period after subsidence of the acute infection.

LABORATORY FINDINGS

• As in Weil's disease, there is usually a leukocytosis with a predominance of polymorphonuclear cells. A mild anemia of the secondary type may develop during the disease. Generally the laboratory findings characteristic of infectious hepatitis are present. The van den Bergh reaction is of little aid and varies remarkably from case to case. In many cases the urine shows albuminuria and cylindruria of mild proportions, but in cases complicated by renal involvement the urinary findings typically seen in acute hemorrhagic nephritis are present. Rarely azotemia may develop. When meningeal signs are present there is usually a mild increase in the cerebrospinal fluid pressure. The cerebrospinal fluid is clear and usually weakly positive for albumin. There may be up to 300 white blood cells in the fluid; at first polymorphonuclear cells predominate, but soon the lymphocyte becomes the predominating cell. According to Walch-Sorgdrager^{15a} the chlorides may be slightly down and the sugar slightly elevated. The cerebrospinal fluid is occasionally bloody. *Leptospiras* may be present in the fluid. The cerebrospinal fluid may show these characteristics in the absence of any clinical evidence of meningeal irritation.

Unlike Weil's disease, dark field examinations of the blood for *leptospiras* are thought to be useless. Experience is needed for accuracy

in making dark field examinations of blood for leptospiras, or else pseudospirochetes due to fibrin and degenerating blood cells described by Schultz¹⁹ may be mistaken for them. On the other hand, leptospiras can frequently be seen in the patient's urine between the tenth and the thirtieth day of the disease if certain precautions are taken. According to Ashe and his associates²⁰ best results can be obtained in dark field examination of urine if the urine used is less than one hour old and approximates neutrality in reaction. *L. canicola* is identical morphologically to *L. icterohaemorrhagiae* even by electron microscope.²¹ The leptospiras are 4 to 10 microns long and contain no granules, internal structure or flagellae. They may have a hook on one or both ends. All progression is in the direction of the straight end and by a rotary motion of the hooked end. If both ends are hooked there is no progression. It has been said²² that *L. icterohaemorrhagiae* can be differentiated from other blood spirochetes by its insolubility in a 10 per cent solution of saponin. No data were found on the reaction of the 10 per cent solution of saponin on *L. canicola*.

Brown and Davis²³ described an adhesion test for the differentiation of leptospiras. A complement fixation test for the same purpose was described by Gaetgens²⁴; however, these tests are not generally used, nor are they as valuable as the agglutination-lysis test of Schüffner. They offer no additional information when they are used. The agglutination-lysis test is designed to show the presence of antibodies in the serum of the patient against the leptospiras suspected of causing the infection. With proper antigens it can be used with equal value in testing for either Weil's disease or canicola fever. According to Raven²⁵ seven day old cultures of *L. canicola* grown on Schüffner's modification of Verwoort's medium are best to employ as antigens. Some investigators claim that it is best to use live cultures, but equally good results

19. Schultz, E. W.: Pseudospirochetes Derived from Red Blood Cells, *J. Lab. & Clin. Med.* 8:375-381 (March) 1923.

20. Ashe, W. F.; Pratt-Thomas, H. R., and Kumpe, C. W.: Weil's Disease: Complete Review of American Literature and Abstract of World Literature; Seven Case Reports, *Medicine* 20:145-210 (May) 1941.

21. Morton, H. E., and Anderson, T. F.: Morphology of *Leptospira Icterohaemorrhagiae* and *L. Canicola* as Revealed by Electron Microscope, *J. Bact.* 45: 143-146 (Feb.) 1943.

22. Bertucci, E. A., Jr.: Leptospirosis, *Am. J. M. Sc.* 209:86-111 (Jan.) 1945.

23. Brown, H. C., and Davis, L. J.: The Adhesion Phenomenon as an Aid to the Differentiation of *Leptospira*, *Brit. J. Exper. Path.* 8:397-403 (Oct.) 1927.

24. Gaetgens, W.: Die Serodiagnose der Weilschen Krankheit mittels Komplementbindungs- und Flockungs-reaktion, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 79:428-451, 1933.

25. Raven, C.: Canine Leptospirosis in Pennsylvania, *J. Infect. Dis.* 69: 131-137 (Sept.-Oct.) 1941.

can be obtained from freshly formalized cultures. Agglutination occurs when the antibodies are concentrated in the serum being tested, but when the end point is approached only lysis occurs. Prozone phenomena may occur. Anamnestic reactions have been reported, and false positive reactions rarely occur. A negative agglutination-lysis reaction thirty days after the onset rules out the disease. Raven's article²⁵ is especially recommended for information concerning the preparation of Schüffner's modification of Verwoort's medium, for the method of obtaining anti-serum and for the technic of performing the agglutination-lysis test. Antibodies against *L. canicola* appear about the tenth day of the disease and reach their maximum about the thirtieth day. The titer may remain elevated for many years but usually falls to 1:300 in two to three years. There is mild cross agglutination between *L. canicola* and *L. icterohaemorrhagiae*, but there is rarely any difficulty in determining which is the offending organism. Rarely, repeated agglutinations at intervals of a few days are required to determine the causative leptospira. Since *L. icterohaemorrhagiae* and *L. canicola* are identical morphologically and since the clinical pictures of canicola fever and Weil's disease are so similar, it is impossible to differentiate between the two except by serologic means. Mild cross agglutinations between *L. canicola* and *Leptospira hebdomadis* have also been reported.⁸ The article of Meyer and his associates¹⁷ also contains useful information concerning laboratory technics. The diagnosis of canicola fever generally has been made by the agglutination-lysis test, and certainly the diagnosis always has been confirmed by it. There is no commercial antigen that gives consistently dependable results, and investigators generally prepare their own antigens. Antibodies against *L. canicola* may be present in the cerebrospinal fluid, but they are usually present in a lower titer than that found in the serum. Leptospiras may be found in the cerebrospinal fluid, and Fontana's stain is best used in the search for them. Levaditi's stain is used when one is searching for leptospiras in tissues.

L. canicola can be isolated from the urine if proper care is employed. It is best to use fresh, centrifuged, neutral urine for inoculation of Schüffner's modification of Verwoort's medium. Five to six weeks may be required for growth of the organism. Leptospiras apparently grow best in a narrow zone just below the surface of the medium where the oxygen tension is somewhat reduced. The optimum temperature for growth has been said to be 25 to 30 C.²² Care must be employed in the selection of test animals to be used in the isolation of *L. canicola*. Rabbits, white mice, rats, field mice and cats are poor test animals. They rarely, if ever, become infected, and the leptospiras cannot be isolated from their blood. According to recent reports²⁶ hamsters and

26. Meyer, Eddie and Stewart-Anderson.⁴ Randall and Cooper.^{12a} Larson.^{12b} Morton.¹⁶

guinea pigs are the best animals to employ. In contrast to *L. ictero-haemorrhagiae*, *L. canicola* may not infect guinea pigs, and even if the guinea pigs become infected they may not become jaundiced and die (especially if there have not been repeated, serial passages). It is reported¹⁶ that 0.5 cc. of a live culture of *L. canicola* injected subcutaneously into 3 to 5 week hamsters will infect the animals, and leptospiras may be found in their heart blood after forty-eight, seventy-two or ninety-six hours, although the animals survive. With *L. canicola* of greater virulence death of the hamsters may occur in nine to ten days.^{12a} *L. icterohaemorrhagiae* invariably causes death in hamsters in about five days.

DIFFERENTIAL DIAGNOSIS

Naturally the differential diagnosis is the same as that of Weil's disease, since both have similar clinical pictures. This differentiation is made by serologic means. A history of exposure to contamination with dog's urine is of great value in diagnosing canicola fever. Such a history has been obtained in approximately 50 per cent of the cases reported thus far. The commonest confusion in leptospiral infections is with common infectious hepatitis. The high white blood cell count, rapid onset, absence of splenomegaly and lymphadenopathy, more rapidly appearing and deeper jaundice, hemorrhagic tendencies, meningeal, pneumonic and nephritic manifestations and a history of possible exposure to contamination with leptospiras should suggest that a patient is suffering from a leptospiral infection. Typhoid may give some difficulty in differential diagnosis, but this differentiation is made through the difference in the incubation periods of the two diseases, the absence of calf tenderness in typhoid and the absence of abnormalities of the cerebrospinal fluid in typhoid. Influenza may at times be confused with canicola fever. Yellow fever, relapsing fever, black-water fever, syphilis of the liver, hepatic abscess and acute yellow atrophy have been included in the differential diagnosis for leptospiral infections. A lengthy discussion of the clinical variations between canicola fever and the disorders listed does not appear to be warranted, since a diagnosis of canicola fever certainly cannot be established, owing to the lack of a constant and well defined clinical syndrome, until laboratory evidence is obtained. Laboratory tests should always be run when the history or clinical features of a case suggest that *L. canicola* may be causing the illness.

EPIDEMIOLOGY

In approximately 50 per cent of cases it has been possible to trace the source of infection to an infected dog. Dogs infected with the disease excrete the organisms in their urine. It is generally thought that dogs exhibit leptospiruria for only a few months; however, Meyer and his

associates¹⁴ stated their belief that a chronic nephritis may develop from the infection and cause the dog to shed leptospiras for many months. Human beings become infected by contacting broken skin or intact mucous membrane with material contaminated with living leptospiras. The organisms will not penetrate intact skin. Consequently, the disease is an industrial hazard of veterinarians and dog catchers. Children often get the disease by playing with an infected dog. There is no instance on record of transmission of the disease from one human being to another.

The incubation period of the disease is unknown; however, it is thought to be the same as that of Weil's disease, roughly one to two weeks.

Although *L. icterohaemorrhagiae* is known to infect many animals (dogs, field mice, cats, pigs, foxes, mongooses, poultry, bandicoots, horses and rats²²), *L. canicola* has never been shown to infect any animal naturally but the dog. The dog, nevertheless, is capable of carrying *L. icterohaemorrhagiae*, *leptospira hebdomadis* (in Java) and the Australian type of *Leptospira* "Ballico" in Celebes.¹⁷

It is known that leptospiras are capable of surviving and remaining virulent for a period of three weeks in stagnant water that has a reaction that approaches neutrality.²² The organisms normally die at a p_H below 6.7. There is a nonvirulent type of leptospira, *Leptospira biflexa*, which is similar to *L. icterohaemorrhagiae* and *L. canicola* morphologically. Some investigators have suggested that under proper conditions a nonpathogenic leptospira, such as *L. biflexa*, may change into a pathogenic leptospira, such as *L. icterohaemorrhagiae* or *L. canicola*. Bertucci²² stated that Inada believes an infective, granular form of leptospira exists.

Leptospirosis *canicola* is a common and serious disease in dogs. Generally speaking, 4 to 15 per cent of dogs the world over have a titer against *L. canicola* of 1:100 or over. Much higher values have been obtained. Twenty-five per cent of Northern California dogs¹⁷ gave positive agglutinations to *L. canicola*, and 19 per cent of the dogs of Southern California,^{12c} while 38.1 per cent of 105 rural dogs from Pennsylvania had agglutination titers to *L. canicola* of 1:300 or better.²⁵ It is known that the percentage of positive titers to *L. canicola* increases with the age of the dogs tested. About 90 per cent of dogs over 6 years of age have positive reactions to *L. canicola*. More males are infected than females, and this is possibly due to the habit of male dogs of sniffing the genitals of other dogs. There is evidence to suggest that the disease can be transmitted from one dog to another by intercourse. There are more dogs infected with *L. canicola* than with *L. icterohaemorrhagiae*. Raven²⁵ gave a table of the prevalence of canine leptospirosis the world over.

The disease in dogs has been called Stuttgart's disease or dog typhus. According to Meyer and his associates¹⁴ the disease may take two forms in dogs. There may be considerable hepatic damage with jaundice, "the yellows" (33 per cent of cases), or there may be an extreme hemorrhagic gastroenteritis without jaundice, Stuttgart's disease (34 per cent of cases). In some cases both types of the disease are seen in the same dog at different stages of the disease. Dogs are more likely to become jaundiced when infected with *L. icterohaemorrhagiae* than with *L. canicola*; however, they are more likely to die in uremia if the infecting organism is *L. canicola*. The mortality in dogs has been said to be as high as 50 to 80 per cent, but this certainly does not include many cases of mild disease which undoubtedly occur. The fact that many subclinical cases in dogs occur is supported by the high percentage of dogs which are serologically positive to *L. canicola* and by the fact that experimental efforts to infect dogs have produced only subclinical infections.

There is undoubted evidence, as already stated, that subclinical cases of canicola fever occur in human beings. One would, therefore, expect routine agglutinations to demonstrate a certain percentage of persons with agglutinins in their serum against *L. canicola*. This has not been the case in the studies so far carried out. Tiffany and Martorana²⁷ found no titers against *L. canicola* in the serums of 59 persons whose activities were such as to bring them into contact with dogs. Greene^{12c} found the serums of 426 persons who had close contact with dogs to have no antibodies against these leptospiras. Although the percentage of rats infected with *L. icterohaemorrhagiae* is roughly the same as the percentage of dogs infected with *L. canicola*, a small but definite percentage of the entire human population have titers against *L. icterohaemorrhagiae*, although they may not recall ever having had symptoms of Weil's disease. This percentage becomes remarkably high when the persons tested are rat catchers, fish workers, and the like—sometimes approaching 50 per cent. This variation is partly explainable in that food and water are not so frequently contaminated by dogs as by rats. Also, rats shed leptospiras for the rest of their lives once they are infected, whereas it seems that dogs are relatively transient shedders of *L. canicola*. The fact that the urine of a dog is usually rather acid in reaction, and thus will tend to kill leptospiras, may also help to explain the rarity of canicola fever. It may be, however, that once canicola fever becomes better recognized it will be found more often.

Preventive measures, such as acidification of stagnant water, as used against Weil's disease are not practical against canicola fever since so

27. Tiffany, E. J., and Martorana, N. F.: Leptospirosis in New York City: Serological Survey, *Am. J. Hyg.* **36**:195-204 (Sept.) 1942.

few cases have been reported. It is necessary, however, to isolate an infected dog until he stops showing leptospiras in his urine. It also is likely that more cases of canicola fever would be discovered if members of a family possessing a dog infected with *L. canicola* were routinely tested for antibodies in their serums.

TREATMENT

In the past the treatment of canicola fever has been the same as that used in any acute infectious hepatitis—namely, symptomatic therapy and dietary and vitamin therapy designed to protect the liver. No specific therapeutic agents have been used with success in the disease in human beings. Sulfonamide compounds have been shown experimentally and clinically to have no effect against either Weil's disease or canicola fever. Arsenicals are dangerous and ineffective. There is some evidence to indicate that penicillin will prove useful in the treatment of both these diseases. Recently Alston and Broom²⁸ showed that penicillin had both lethal and inhibitory effects in vitro on nine strains of *L. icterohaemorrhagiae* and one strain of *L. canicola*. It cured leptospirosis icterohaemorrhagica in guinea pigs if given early and in large doses; however, the drug did not prevent the development of antibodies against the leptospiras. It is suggested that penicillin would have the same effect against leptospirosis canicola in animals. There are a few reports in the literature²⁹ of Weil's disease treated with penicillin, and in general it seems that penicillin is useful if given in large doses early in the disease. It would appear likely that penicillin would have the same effect on canicola fever if the same conditions were met. Bismuth compounds have been used on the Continent³⁰ with apparently good results. There is no instance of their being used against canicola fever.

Although antiserum against *L. icterohaemorrhagiae* infections in man has been used with success abroad,³¹ no similar antiserum has been used against canicola fever. *L. canicola* antiserum¹⁷ has given striking success in the disease in dogs if given early in the course of the disease.

28. Alston, J. M., and Broom, J. C.: Action of Penicillin on *Leptospira* and on Leptospiral Infections in Guinea Pigs, *Brit. M. J.* **2**:718-719 (Dec. 2) 1944.

29. Carragher, A. E.: Case of Weil's Disease Treated with Penicillin, *Brit. M. J.* **1**:119 (Jan. 27) 1945. Bulmer, E.: Weil's Disease in Normandy: Its Treatment with Penicillin, *ibid.* **1**:113-114 (Jan. 27) 1945.

30. Uhlenhuth, P., and Seiffert, A.: Untersuchungen über die Ausheilung der Weilschen Krankheit bei Meerschweinchen unter der Behandlung mit Bismuto-Yatren A, *Zentralbl. f. Bakt. (Abt. 1)* **114**: 241-251 (Oct. 31) 1929.

31. Inada, R.: Prophylaxis and Serum Treatment of *Spirochaetosis Ictero-haemorrhagiae*, *Japan M. World* **2**:189-193 (July) 1922. Walch-Sorgdrager,^{15a}

Human beings have been vaccinated against Weil's disease³² with homologous vaccine with definite benefit. No such attempt has been made against canicola fever because of its rarity. Animals can certainly be protected against *L. icterohaemorrhagiae* if they are inoculated with killed or nonvirulent *L. icterohaemorrhagiae*. Some investigators say that there is no cross protection between *L. icterohaemorrhagiae* and *L. canicola*,³³ while others³⁴ claim that there is.

It can be said that whatever specific treatment that is used against canicola fever should be given early. At present most of the diagnoses are made serologically, and consequently late in the course of the disease. It is unlikely that any specific therapy will be of value until the presence of the disease is appreciated sufficiently by the medical profession so that a diagnosis will be made early.

SUMMARY

A case of canicola fever, or leptospirosis canicola, is reported. The literature is reviewed relative to the history, incidence, clinical features, laboratory findings, epidemiology and treatment of the disease.

32. Das Gupta, B. M.: Observations on Some Immunological Aspects of *Leptospira Icterhemorrhagiae*: Development of Active Immunity in Many Following Injection of *Leptospira* Vaccine, *Indian M. Gaz.* **77**: 28-29 (Jan.) 1942.

33. Larson, C. L.: Protection Test in Mice for Identification of *Leptospira Icterohemorrhagiae* (Weil's Disease), *Pub. Health Rep.* **56**:1593-1609 (Aug. 8) 1941.

34. Smith, J.: Vaccination of Guinea-Pigs and Human Beings Against Leptospiral Infections, *J. Hyg.* **37**:261-270 (April) 1937.

CLINICAL ASPECTS OF CALCIFICATION OF THE MITRAL ANNULUS FIBROSUS

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CALCIFICATION of the mitral annulus fibrosus has been studied by pathologists¹ and is fairly often discovered more or less accidentally during life by radiologists.² Both groups of observers, properly enough, have regarded it as a degenerative change of no clinical significance.

Yet such calcification is not entirely without clinical interest and was in part the subject of a recent monograph.³ Its occurrence in the older age groups guarantees that it will be associated at least now and then with obvious heart disease⁴; in fact, it has long been known⁵ as one variety of those calcifications which cause heart block.⁶

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1. (a) Geerling, J. G.: *Sclerosis annularis valvularum*, Thesis, Groningen, Leeuwarden, B. B. Westerhuis, 1929. (b) Giese, W.: *Die Verkalkungen des Herzskeletts*, Beitr. z. path. Anat. u. z. allg. Path. **89**:16-39, 1932. (c) Ribbert, H.: *Die Erkrankungen des Endokards*, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1924, vol. 2, p. 184. (d) Martens, G.: *Beziehungen zwischen der Verkalkung des Annulus fibrosus der Mitralklappen und anderen regressiven Erscheinungen*, Beitr. z. path. Anat. u. z. allg. Path. **90**:497-502, 1932.

2. (a) Sosman, M. C.: *The Technique for Locating and Identifying Pericardial and Intracardiac Calcifications*, Am. J. Roentgenol. **50**:461-468 (Oct.) 1943; (b) Sosman, M. C.: *Subclinical Mitral Disease*, J. A. M. A. **115**:1061-1066 (Sept. 28) 1940. (c) Sundberg, C. G.: *Kymographische Untersuchung eines Herzens mit verkalktem Annulus fibrosus*, Acta radiol. **22**:834-840, 1941. (d) Roesler, H.: *Clinical Roentgenology of the Cardiovascular System*, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1943, p. 265.

3. Menezes de Oliveira, R.: *Escleroses valvulares calcificadas*, Rio de Janeiro, Tipografia do Patronato, 1943; reviewed, Am. Heart J. **29**:139 (Jan.) 1945.

4. Marks, J. H.: *Calcification in the Annulus Fibrosus of the Mitral Valve*, New England J. Med. **214**:411-414 (Feb. 26) 1936.

5. Cowan, J., and Ritchie, W. T.: *Diseases of the Heart*, ed. 2, London, Edward Arnold & Co., 1922, p. 122.

6. Yater, W. M., and Cornell, V. H.: *Heart Block Due to Calcareous Lesions of the Bundle of His: Review and Report of a Case with Detailed Histopathologic Study*, Ann. Int. Med. **8**:777-789 (Jan.) 1935.

Then too either the calcification itself or the accompanying valvular changes of aging might reasonably be expected to alter cardiodynamics even in the absence of heart block; practically nothing⁷ has been written about murmurs in its presence, and prominent authors⁸ dismiss it somewhat vaguely as occasionally associated with mitral regurgitation and an apical systolic murmur.

The primary purpose of this paper is to present observations made during the lives of 10 elderly patients with calcification of the mitral annulus fibrosus; our own interest in this disorder was aroused by the heart block found in the electrocardiograms of 5 of these patients and by the nature of the murmurs heard in their hearts.

REPORT OF CASES

CASE 1.—Mrs. M. L. was 74 years of age when dyspnea brought about her admission to Stanford University Hospitals on May 30, 1938. She had never had rheumatic fever but had been told of the presence of a murmur when she was 56.

She was small, dyspneic and orthopneic. Signs of moderate passive congestion were present. The arterial pressure averaged about 200 mm. during systole and 90 mm. in diastole. The heart was enlarged some 2 cm. to the left, and its beats were regular at a rate of 45 per minute. A loud rather coarse systolic murmur, best heard along the left sternal border from the second to the fifth rib, was transmitted to the apex as well as to the aortic area and the carotid arteries; there was no thrill. The apical first sound varied in intensity.

Auricular sounds heard at the apex were at first thought to be the usual sounds audible in patients with complete heart block; later they were discovered to be murmurs (see third paragraph following).

An electrocardiogram showed complete heart block and left bundle branch block. Roentgenograms showed pulmonary congestion, much calcification in the aorta and moderate cardiac enlargement.

Improvement followed rest in bed and the use of diuretics, sedatives and digitalis. In the electrocardiograms, the bundle branch block soon disappeared, not to return until 1941; sinus rhythm was recorded three times in June and July of 1938, with P-R intervals of 0.19, 0.20 and 0.21 second; the supernormal phase of conduction (P-R, 0.16 second) was present once in the same period; later 2:1 block was present almost as often as complete block, and auricular fibrillation appeared for two months in 1941. The Stokes-Adams syndrome never occurred. Most of the time the patient sat up at home and was even ambulatory. Edema returned in 1941 but was controlled by mercurial diuretics. She died soon after the occurrence of clonic movements in the right arm and leg on July 2, 1943, at the age of 79; permission for necropsy was refused.

When the patient came to the laboratory in 1939 for the purpose of having the heart sounds in complete block recorded, Dr. J. K. Lewis pointed out during

7. Libman, E., in discussion on McGinn, S., and White, P. D.: Valvular Atherosclerosis, *Am. Heart J.* 10:404-405 (Feb.) 1935.

8. (a) Levine, S. A.: *Clinical Heart Disease*, ed. 3, Philadelphia, W. B. Saunders Company, 1945, pp. 39 and 227. (b) Osler, W.: *Principles and Practices of Medicine*, edited by H. A. Christian, ed. 15, New York, D. Appleton-Century Company, Inc., 1944, p. 1052.

auscultation that the apical sound heard during ventricular diastole was in reality a murmur. This was confirmed by a phonocardiogram (fig. 1 *A*), which showed the relation of the murmur to the P wave; the murmur with ventricular systole and the variation in intensity of the first heart sound were also demonstrated.

The murmur confined to the apex was best heard with the patient recumbent, particularly in the left lateral position. It was of blowing quality and never loud although readily audible. Varying greatly in intensity, it was faintest just before ventricular systole and loudest during a period near early ventricular diastole. When 2:1 block was present, the murmur was heard only with the blocked auricular systole and was scarcely recorded with the conducted one (P-R, 0.24

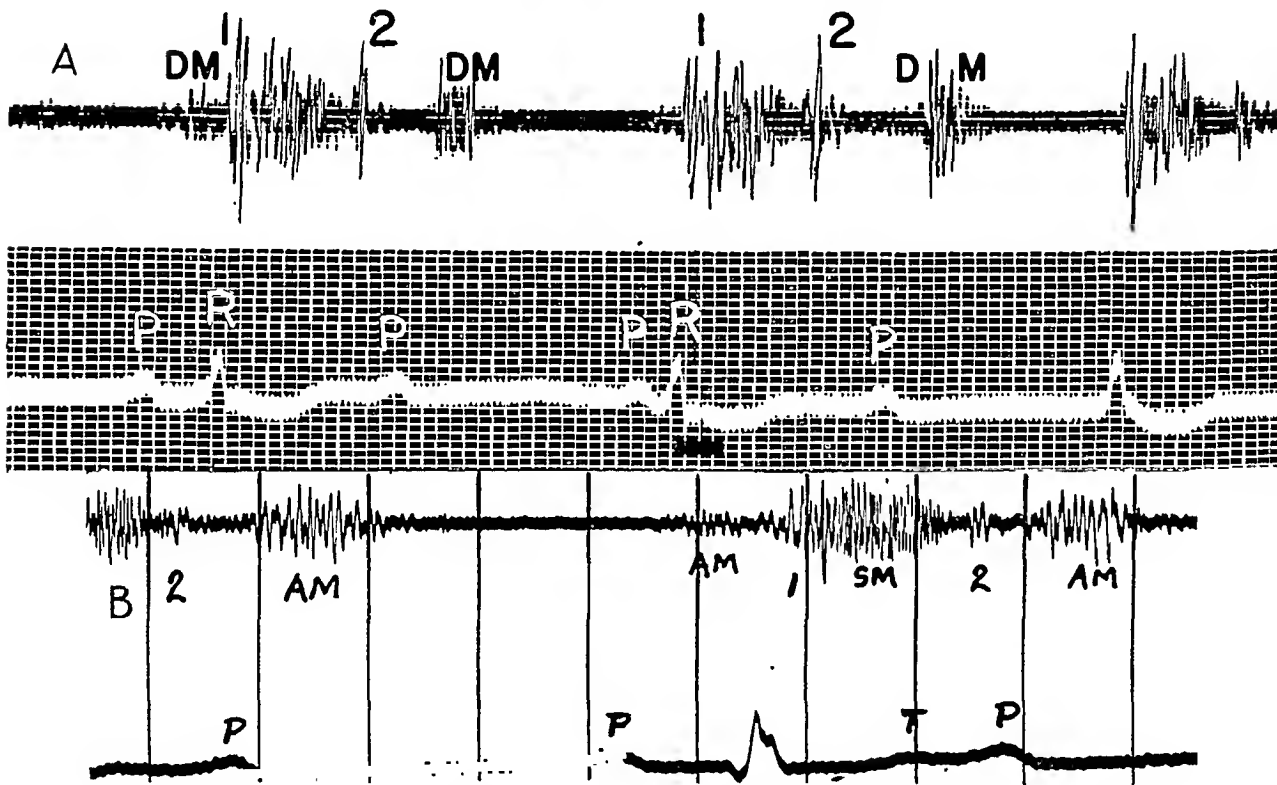


Fig. 1.—*A* (case 1), heart sounds at the apex with simultaneous electrocardiogram in the presence of complete auriculoventricular block. *DM* designates the murmur with auricular activity and *1* and *2* the first and second heart sounds. Short black bar locates maximum vibrations of an intense first sound with short P-R interval. (Time markings in all phonocardiograms are 0.04 and 0.20 second). *B* (case 2), heart sounds at the apex (above) with simultaneous electrocardiogram. *AM* designates auricular murmur, *SM* the murmur with ventricular systole and *1* and *2* the first and the second heart sounds.

second); with auricular fibrillation, the murmur was audible and recorded early in diastole.

Fluoroscopic examination with Dr. Edward Leef in November 1939 showed the heart to be smaller than before and of practically normal size; the left auricle was not prominent, and a nearly complete ring of calcification was seen in the region of the mitral annulus fibrosus, moving toward the apex with ventricular systole. The calcification was visible in films. These observations were later repeatedly confirmed.

Summary.—A woman of 74 was found to have congestive heart failure and complete auriculoventricular block. There was a loud, coarse murmur, best heard at the left sternal border with ventricular systole; there was also a fainter apical blowing murmur with auricular activity. Calcification of the mitral annulus fibrosus was seen with the fluoroscope and in roentgenograms, but there was no enlargement of the left auricle. Meanwhile, complete heart block temporarily gave way at various times to sinus rhythm with normal conduction and to 2:1 block; it was at times complicated by left bundle block and by auricular fibrillation. With the latter, the apical murmur was found in early diastole. Congestive failure was controlled with diuretics and digitalis. The patient died at the age of 79 of cerebral vascular disease.

CASE 2.—Mr. P. B. was 65 when he first visited Stanford Out-Patient Clinics, March 25, 1940, because of dyspnea and angina pectoris. He had not had rheumatic fever but had known of a murmur for years.

Examination showed a large man who did not appear to be ill. There were no signs of congestive failure. There was only moderate thickening of the radial arteries, and the retinal vessels were practically normal. The arterial pressure was 135 mm. in systole and 90 mm. during diastole. The heart was not enlarged. The beats were regular at a rate of 84 per minute. Over the precordium, loudest at the base, was heard a fairly loud, rough systolic murmur; diastole was clear. No thrill was felt. The electrocardiogram showed sinus rhythm, P-R interval of 0.22 seconds and left axis deviation with normal T waves.

The patient's symptoms improved with the use of glyceryl trinitrate and phenobarbital. A year later the conduction time was only 0.18 second. In March 1943 he again became dyspneic; digitalis was administered in the usual dosage when basal rates were heard. Two weeks later complete heart block was present temporarily, followed by 3:2 auriculoventricular block.

On examination, March 24, 1943, one heard a loud, rough murmur with ventricular systole, best at the base, but transmitted to the carotid arteries and to the apex; there was also a fainter rough blowing murmur at the apex with auricular activity, loudest when that event occurred early in ventricular diastole (fig. 1 *B*). The apical first sound varied in intensity from cycle to cycle. Fluoroscopic examination repeatedly showed a densely calcified ring in the region of the mitral annulus fibrosus; this was recorded in films. The left auricle was not dilated; the heart was slightly enlarged.

With smaller amounts of digitalis, sinus rhythm returned but with P-R intervals of 0.23 to 0.32 second; with such prolonged conduction times which persisted even during the temporary withdrawal of digitalis, the apical murmur was found only in late ventricular diastole.

In 1944 and 1945 congestive failure and auricular fibrillation appeared, and the heart and its left auricle enlarged. With this arrhythmia, the apical murmur became fainter, was not audible except when the patient was in the recumbent position and was confined to early diastole. The patient died of congestive failure on June 2, 1945; permission for necropsy was refused.

Summary.—A man of 68 with mild congestive failure and angina pectoris had a loud, rough precordial systolic murmur; the slightly prolonged conduction time later became normal temporarily. When digitalis was followed by complete heart block, an apical murmur related to auricular activity was heard and recorded. The heart was slightly enlarged but the left auricle was not dilated at the time of the fluoroscopic examinations in which a calcified mitral annulus fibrosus was seen. With less digitalis and even without it, complete heart block was replaced

by sinus rhythm with prolonged conduction time; under these conditions the apical murmur was present only late in diastole. Congestive failure finally increased, in spite of the use of digitalis: The heart and its left auricle became dilated, and auricular fibrillation appeared, whereupon the apical murmur diminished in intensity and was confined to early diastole. The patient died at the age of 70, of congestive heart failure.

CASE 3.—Mrs. L. B. was 68 years of age when she entered San Francisco Hospital in 1939 for dyspnea on exertion; the complete heart block found at that time persisted throughout the rest of her life.

In 1941 we examined her because of dizziness on turning the head from side to side. There was no history of rheumatic fever. She was alert, elderly and slightly obese. There was evidence of peripheral and retinal arteriosclerosis. Arterial pressure was 270 mm. in systole and 110 mm. in diastole. The lungs were clear. The heart beats were regular at a rate of 48, and the heart was enlarged to the anterior line. A thrill at the base corresponded to a loud systolic murmur there, transmitted to the apex and into the carotid arteries. The first

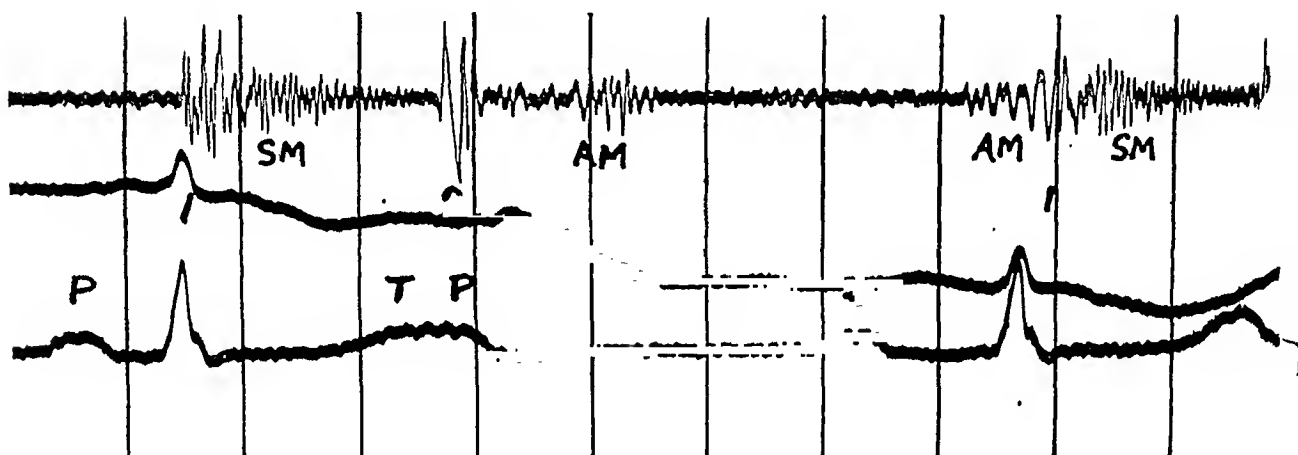


Fig. 2 (case 3).—Heart sounds at the apex (above) with simultaneous electrocardiogram (below) during complete auriculoventricular block. Ignore the irregular middle tracing. *AM* designates the murmur with auricular activity, *SM* the murmur with ventricular systole, 1 and 2 the first and the second heart sounds. Note the absence of auricular murmur after the first *P* wave, with *P*-*R* interval of only 0.20 second.

heart sound varied in intensity. There was a soft blowing apical murmur heard during ventricular diastole, especially early in diastole and particularly with the patient in the left lateral recumbent position; phonocardiograms (fig. 2) showed this murmur to be related to the *P* wave.

Roentgenograms revealed an enlarged heart, with no particular left auricular dilatation, and calcification of the mitral annulus fibrosus (fig. 3).

Angina pectoris began in May 1942, and the patient died of myocardial infarction four months later.

At necropsy, performed in the department of pathology of Stanford University, the heart weighed 420 Gm. The wall of the left ventricle was extremely thick, and there was a region of myocardial infarction posteriorly. The coronary arteries showed moderate diffuse sclerosis and narrowing without demonstrable acute occlusion. The aortic, the pulmonary and the tricuspid valves were normal. There was extensive calcification of the mitral valve ring forming a rigid band

about 1 cm. in thickness and 9 cm. in circumference (fig. 4 *A*), which extended into the bases of the cusps and there caused some distortion; near their free margins, however, the leaflets were normal. The chordae tendineae were normal. There was slight, diffuse endocardial thickening of the left auricle but no striking dilatation. The calcified mass extended well into the posterior part of the membranous portion of the interventricular septum.

There was pronounced aortic atherosclerosis. The orifices of the innominate and the left carotid arteries were nearly occluded by a gray firm mass, about 2 cm. long, adherent to each vessel wall (fig. 4 *B*). There were two scars of old healed duodenal ulcers.

Microscopic examination showed the near occlusion of these aortic branches to be due to extensive intimal thickening. The thickened area showed consider-



Fig. 3 (case 3).—A roentgenogram of the chest, oblique view, showing calcification of the mitral annulus fibrosus (not to be confused with that of the cartilages of the ribs).

able fibrous tissue and much calcium, covered by a layer of intima. The endocardium of the left auricle was thickened. The aortic valve leaflets were slightly thickened by collagenous fibrous tissue; the mitral leaflets contained small flecks of calcium in addition to being similarly thickened. Pulmonary and coronary arteries contained calcified intimal plaques; the coronary lumens were small. Calcification in the mitral annulus fibrosus destroyed much of the underlying muscle, including some of that forming the interventricular septum. In the latter region the small arteries showed extensive arteriosclerosis but no actual occlusion. No Aschoff bodies were seen.

Summary.—A woman with mild congestive failure and complete heart block for three years died at the age of 72, after myocardial infarction. An apical mur-

mur related to auricular activity was recognized as such and recorded. The calcified mitral annulus fibrosus found at necropsy was seen in roentgenograms; the calcification invaded the interventricular septum and distorted the bases of the mitral leaflets. A thrill and murmur occurred at the base with ventricular

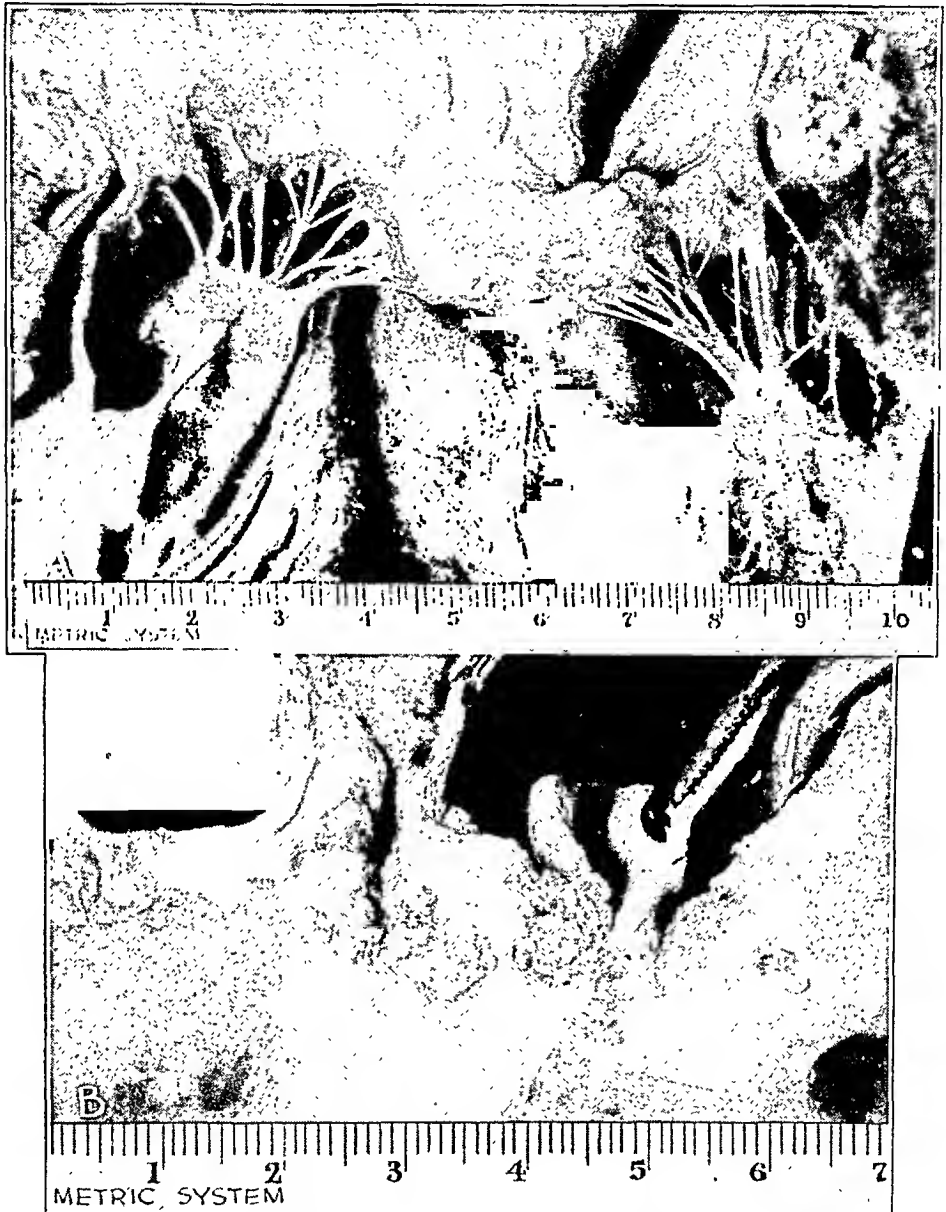


Fig. 4 (case 3).—*A*, a region of the mitral valve, with cross sections of the calcified lesion near the upper corners. *B*, lesions in the opened aorta and the innominate and left carotid arteries.

systole. Massive calcifications were found in the greatly thickened intima of the innominate and left carotid arteries; the aortic valve was virtually normal.

CASE 4.—Miss R. A. was a tiny woman of 73, in 1936, when dyspnea led to the discovery, at the Laguna Honda Home, of complete heart block. She had never

had rheumatic fever. The tibias were much bowed with osteitis deformans, and she was partially deaf and blind. Moderate edema of the legs was the only sign of congestion. Peripheral arteriosclerosis was advanced. The arterial pressure was 220 mm. in systole and 70 mm. in diastole. The heart, with regular beats at a rate of 46 per minute, was enlarged to the anterior axillary line. A moderately loud, rough systolic murmur was heard over the precordium, loudest along the left sternal border; there was no thrill.

Rest and digitalis brought improvement. There were no signs of heart failure when the patient was first examined by one of us, in 1942. At that time, heart block was still complete, but cardiac enlargement was not striking. The first heart sound varied in intensity and was followed by a rough systolic murmur, moderate at the left sternal border, faint at the apex and not heard over the carotid artery. During early diastole a short blowing murmur of moderate intensity was audible at the apex; later, in other cycles, it was fainter.

Electrocardiograms showed complete heart block and left axis deviation. Careful radiologic search for intracardiac calcification was not successful. The heart was somewhat enlarged, but there was no dilatation of the left auricle.

Another physical examination, in 1944, revealed similar conditions. Phonocardiograms confirmed the auscultatory signs. Early in ventricular diastole the vibrations of a murmur accompanied auricular activity, while in late diastole there were only small vibrations of uncertain nature. Once again, a thorough roentgenologic study failed to demonstrate calcification.

Still living at Laguna Honda Home, in 1945, at the age of 82 and without cardiac complaints, the patient was temporarily transferred to the San Francisco Hospital for the purpose of demonstrating her physical signs. On this occasion, Dr. Charles E. Grayson succeeded in satisfying himself and several others, at the time of fluoroscopic examination, of the presence of calcification almost completely encircling the mitral annulus fibrosus; the lesion was visible in at least one roentgenogram. The heart was moderately enlarged, and the left auricle was thought to be prominent.

Physical examination showed that the apical diastolic murmur had become rather rumbling; it was present even when the patient sat upright but was louder when she was in the recumbent position. It was not heard more than once in each cycle and was louder early in diastole. Late in diastole a faint double auricular sound was sometimes audible, and there was an occasional loud click when auricular activity coincided with ventricular systole. The previously noted murmur of the latter event was inconspicuous. There were no signs of congestive heart failure.

Summary.—A small woman has been observed for nine years after the onset of complete heart block at the age of 73. Congestive failure, present at first, virtually disappeared. There was only a faint murmur with ventricular systole, loudest at the left sternal border. At the apex, in diastole, a murmur was heard and recorded in phonocardiograms; blowing at first, it became rumbling as time passed. It was louder when early in diastole and faint in the middle of diastole and was represented only by a faint double sound late in diastole. Roentgenographic study was not successful in showing calcification of the mitral annulus fibrosus until recently; the heart has been moderately enlarged, and the left auricle may be increasing in size.

CASE 5.—Mrs. L. T., aged 72, entered Stanford University Hospitals early in 1942 because of dyspnea for three months. There was no history of rheumatic fever. In 1919 she received antisyphilitic treatment because of a gumma and a

positive blood Wassermann reaction. In 1939 the Wassermann reactions of the blood and spinal fluid were negative. Congestive heart failure began with an infection of the upper part of the respiratory tract.

On examination the patient was obese and dyspneic. Rales were heard at the bases of the lungs. The heart was moderately enlarged; the rate of its beats varied abruptly between 34 and 104 per minute several times, and Stokes-Adams attacks occurred. Most of the time complete heart block was present. A fairly loud, rough murmur was heard at the base with ventricular systole, not transmitted into the carotid arteries but audible at the apex; there was no thrill. Auricular sounds were heard at the apex and the lower left sternal border during periods of heart block, but they were not interpreted as murmurs. In phonocardiograms, auricular activity was sometimes associated with sounds, less often



Fig. 5 (case 5).—Phonocardiograms during complete auriculoventricular block (above) and 2:1 block (below). Ignore the central vascular pulsations in each strip. In the upper record the auricular vibrations (*A*) resemble those of sounds; in the lower record they approach the appearance of a murmur, but the only audible murmur was that with ventricular systole (*SM*).

with vibrations which might be interpreted as murmurs (fig. 5). Arterial pressure was 170 mm. during systole and 100 mm. in diastole.

Roentgenograms revealed cardiac enlargement without particular auricular dilatation; calcification of the mitral annulus fibrosus was not discovered. Electrocardiograms showed 2:1 block, complete auriculoventricular block and varying bundle branch block.

Diuretics, propadrine hydrochloride and digitalis were given. Congestive failure improved, and after a month sinus rhythm reappeared, with a P-R interval of 0.20 second in each of seven records taken in the next three months. The patient left the hospital but returned seven months later with severe congestion.

Electrocardiograms showed complete heart block and left bundle branch block, and auricular tachycardia was recorded just before death, on Nov. 15, 1942.

At necropsy, performed in the department of pathology of Stanford University, the heart weighed 560 Gm. The wall of the left ventricle was thick, and there was no myocardial infarction. The coronary arteries were patent, with only a few atheromatous plaques. There was a small area of calcification at the free edge of the anterior cusp of the tricuspid valve. Similar small nodules were found at the free edges of the cusps of the aortic and pulmonary valves, which were otherwise normal. The mitral annulus fibrosus was completely calcified by a ring 0.5 cm. in thickness and 9 cm. in circumference, from which several nodules of calcified material encroached on the membranous portion of the interventricular septum; the chordae tendineae were slightly thickened. There were many calcified nodules along the proximal surface of the mitral cusps near the ring. There was some calcification at the other side of the membranous septum. The auricles were not particularly dilated.

The arch of the aorta was dilated and roughened as if by syphilis and, in addition, presented a large amount of atheromatous sclerosis. The orifices of the innominate and left subclavian arteries were slightly occluded by rough granular deposits of calcium, which differed from the calcified atheromatous plaques. The thoracic aorta was atheromatous without calcification, but the abdominal aorta was calcified as well. There was a scar of an old duodenal ulcer.

Microscopic examination showed calcification of the lowermost part of the membranous septum, with extension of dense fibrous strands among the muscle fibers of the muscular septum. There were deep infiltrations of fat and many large deposits of calcium in the aortic intima. Scar tissue frequently and abruptly replaced elastic tissue in the aorta. The adventitia of the aorta was thickened, but no cellular infiltration was found about the vasa vasorum. No Aschoff bodies were seen.

Summary.—A woman of 72, treated for syphilis, entered the hospital in a state of congestive failure, of which she later died. The heart was enlarged. Its rhythm frequently changed; 2:1 block, complete block, sinus rhythm and complete block again were recorded. Both left and right bundle branch block and, terminally, auricular tachycardia complicated complete heart block. There was a fairly loud, rough systolic murmur at the base with ventricular systole, transmitted to the apex but not into the carotid arteries. Auricular sounds were audible but never were clinically interpreted as murmurs, although phonocardiograms occasionally revealed them as prolonged vibrations. Stokes-Adams attacks were observed. At necropsy there was a calcified mitral ring (not discovered roentgenologically) from which nodules encroached on the membranous portion of the interventricular septum. Small calcified nodules were present on the free edges of cusps of the aortic, pulmonary and tricuspid valves. The left auricle was normal. There was doubtful syphilis but definite atheromatous calcification of the aorta; the orifices of the innominate and left subclavian arteries were slightly occluded by calcified deposits.

CASE 6.—Mrs. A. S. was 58 years old when she first entered Stanford University Hospitals, in 1937, because of dyspnea. There was no history of rheumatic fever. Dyspnea began in 1931, following "bronchopneumonia," and continued until her death in 1943; she was bedridden most of the time. Repeated examinations showed varying degrees of congestive heart failure, always with rales at the bases of the lungs and often with universal rales and wheezes. The arterial pressure was 220 mm. in systole and 120 mm. in diastole, and there was

moderate peripheral arteriosclerosis. The heart was greatly enlarged but with regular beats at rates of 80 to 100 per minute. There was a loud, rough systolic murmur at the base and the apex, loudest at the left sternal border near the third rib; no diastolic murmur was heard or recorded in phonocardiograms, and there was no thrill. A gallop sound was often heard at the apex, and sometimes pulsus alternans was present. Heart block never occurred.

Electrocardiograms always showed sinus rhythm, P-R interval of 0.14 to 0.17 second and QRS duration of 0.08 to 0.09 second, left axis deviation and abnormal T waves, without much change through the years. Roentgenograms showed progressive cardiac enlargement, calcification of the mitral annulus fibrosus and diffuse pulmonary densities radiating from pulsating rounded hilar masses.

At necropsy, in the department of pathology of Stanford University, the heart weighed 640 Gm. and was enlarged in all chambers. There were two tiny adhesions between cusps of the aortic valve, and there was calcification at the base of this valve, with normal free edges. The tricuspid and pulmonary valves were normal. The flaps of the mitral valve and the chordae tendineae were normal except for several flat yellow atheromas on the anterior leaflet. In the mitral ring by the posterior leaflet there was a calcified mass, 3 cm. long and 0.5 cm. thick, which stopped abruptly at the margin of this cusp. One end of the calcified strand was 1 cm. from the uninvolved membranous septum.

There was moderate atherosclerosis of the aorta, with only slight involvement of the coronary arteries. The lungs were fibrotic and emphysematous; all the larger branches of the pulmonary artery were extremely dilated and atherosclerotic.

Microscopic examination showed diffuse myocardial fibrosis and atherosclerosis of the large vessels. The base of the mitral leaflet previously mentioned was fibrotic and calcified, but the cusp itself was practically normal. No Aschoff bodies were seen.

Summary.—A woman aged 64, died after twelve years of congestive heart failure, in which both systemic and pulmonary hypertension played a part. Heart block was not observed. There was a loud, rough systolic murmur over the base and the apex, but diastole was clear. Calcification of the mitral annulus fibrosus was seen in roentgenograms and confirmed at necropsy; the membranous septum was not involved.

CASE 7.—Miss J. M. was only 57 when she first came to Stanford University Out-Patient Clinics in 1917, with mild hyperthyroidism, which was treated successfully with potassium iodide and irradiation. At that time arterial pressure was 175 mm. during systole and 100 mm. during diastole. The heart was not enlarged, and no murmurs were heard. An electrocardiogram showed sinus rhythm, heart beats at the rate of 100 per minute and left axis deviation.

The patient reappeared in 1933 because of weakness. The thyroid gland displaced the trachea. The cardiac findings were unchanged, but in a roentgenogram the mitral annulus fibrosus was calcified.

She disappeared, to return again, in 1944, at the age of 84, with a carcinoma of the left breast. Arterial pressure was 150 mm. in systole and 90 mm. in diastole. There was no cardiac enlargement. The heart beats were regular at a rate of 80 per minute. There was a loud systolic murmur at the left sternal border near the fourth rib but no thrill. There was no diastolic murmur by auscultation and phonocardiograms showed a few presystolic vibrations (fig. 6). Roentgenograms revealed no changes in the calcified mitral ring and no cardiac enlargement (fig. 7).

An electrocardiogram showed sinus rhythm, P-R interval of 0.15 second, QRS duration of 0.07 second and left axis deviation; it was practically identical with one made in 1917.

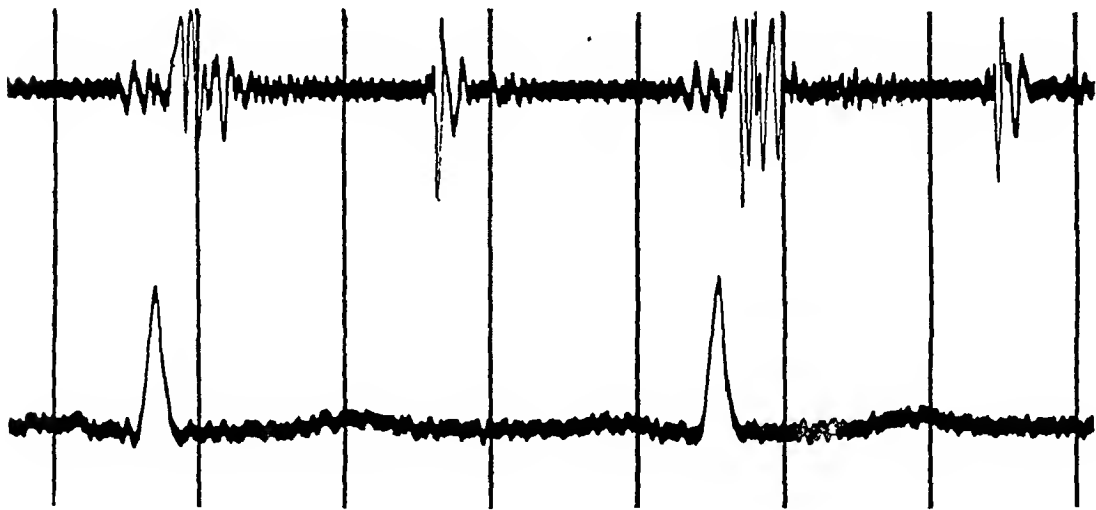


Fig. 6 (case 7).—Heart sounds at apex; presystolic vibrations are present, but no murmur was heard. The vibrations in this case are more prominent than those in cases 6, 8, 9 or 10.

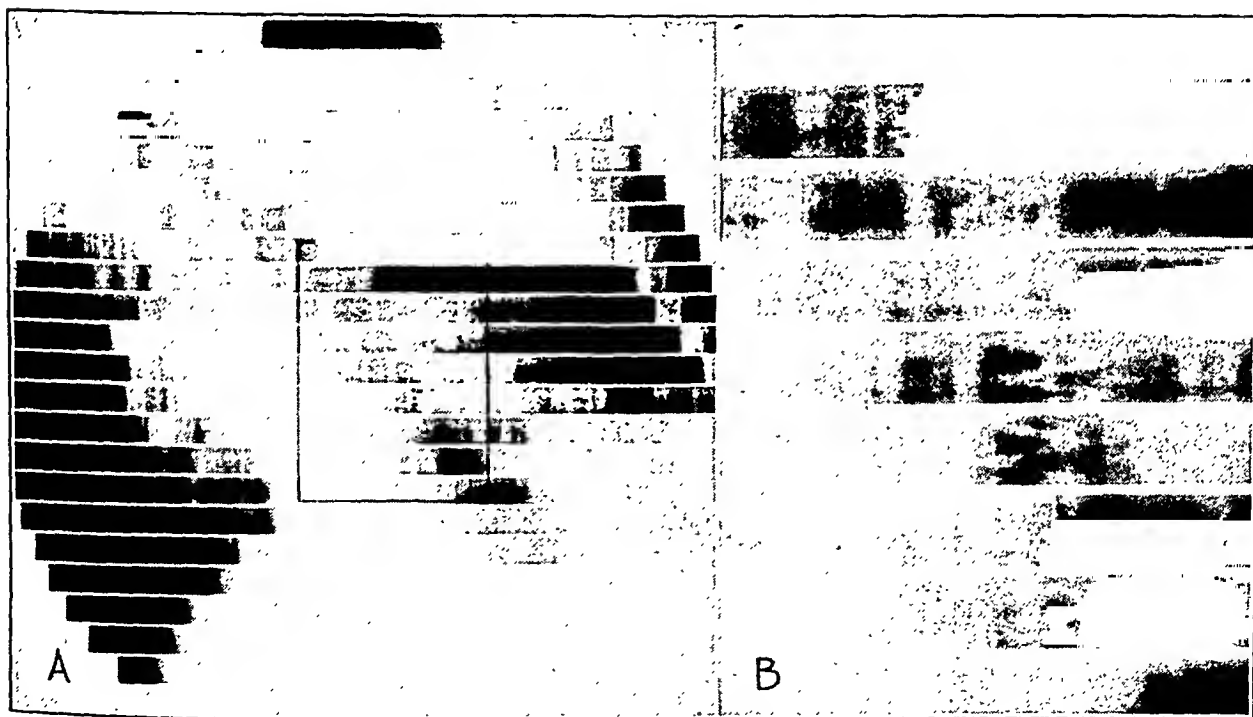


Fig. 7 (case 7).—*A*, a roentgenkymogram in the anteroposterior aspect with the patient standing and grid 45 degrees from horizontal. A rectangle outlines the area (*B*) in which movement of the calcified mitral annulus fibrosus is visible. *B*, movement of the calcified mitral annulus fibrosus; the area is that of the rectangle in *A*.

CASE 8.—Mrs. C. B. came to the Stanford University Out-Patient Clinics in 1944, at the age of 61, because of abdominal pain. Her husband had dementia paralytica. Her blood gave a positive Wassermann reaction but her spinal fluid did not. Arterial pressure was 150 mm. in systole and 90 mm. in diastole. The

heart beats were regular, with a rate of 88 per minute, the heart was not enlarged. There was a transitory and faint systolic murmur all over the precordium, loudest at the left sternal border. Diastole was clear. No murmurs were recorded in phonocardiograms, even when the heart rate was slowed to 50 beats per minute by pressure on the carotid sinus during the administration of digitalis.

An electrocardiogram showed sinus rhythm with P-R interval of 0.14 second, QRS duration of 0.07 second, left axis deviation and normal T waves. Occult blood was found in the stool, and there was slight anemia. During fluoroscopic examination, which revealed irregularity of the duodenal cap, a densely calcified mitral ring was noted.

CASE 9.—Mr. F. F. entered Stanford University Hospitals, at the age of 82, in 1942, because of inability to walk after a cerebral vascular injury; this promptly improved. There was no history of rheumatic fever or syphilis; several Wassermann tests of the blood gave negative results.

The arterial pressure was 240 mm. in systole and 80 mm. during diastole. The heart was slightly enlarged. There was a loud blowing aortic diastolic murmur and a soft systolic murmur along the left sternal border. There was no apical murmur. Pulmonary emphysema was marked.

An electrocardiogram showed sinus rhythm, P-R interval of 0.16 second, QRS duration of 0.08 second and left axis deviation with normal T waves. Roentgenograms revealed a wide tortuous calcified aorta, a prominent left ventricle and a calcification of the mitral annulus fibrosus.

CASE 10.—Mr. C. H., a granite cutter, was 68 when he entered the Stanford University Hospitals in 1936 because of intermittent indigestion for thirty years. He had never had rheumatic fever but had complained of a stiff neck and "sciatica" for many years. The heart was not enlarged, and the beats were regular at a rate of 60 per minute. There was a moderately loud, rough systolic murmur at the apex and the left sternal border, but it was loudest in the aortic area. Diastole was clear. There was no thrill, and the murmur did not reach the carotid arteries. Arterial pressure was 140 mm. during systole and 75 mm. in diastole. The radial arteries were thick and the branchial arteries tortuous. There were a few scattered rales. An electrocardiogram showed sinus rhythm, heart beat rate of 60 per minute, P-R interval of 0.18 second and QRS duration of 0.06 second. Roentgenologic study revealed pneumoconiosis, duodenal ulcer and calcification of the mitral annulus fibrosus; the cardiac shadow was normal in size and shape. Indigestion was relieved by the usual methods. The patient returned in 1944 because of symptoms of disease in the urinary tract; physical observations of the heart were the same as before, and arterial pressure, electrocardiogram and roentgenographic appearance of the heart were all as they had been eight years earlier. Phonocardiograms revealed a few small presystolic vibrations; these were not made any more impressive, nor was a presystolic murmur heard, when the heart rate was slowed to 50 beats per minute and the P-R interval lengthened to 0.20 second by pressure on the carotid sinus after the administration of digitalis.

COMMENT

Ten patients with calcification of the mitral annulus fibrosus were observed during life; the diagnosis was made at necropsy for 1 and by roentgenologic means (confirmed twice at necropsy) for the others.

Sex and Age.—Seven of the 10 patients were women. In a much larger series³ of similar patients there were also 2 women to every man;

in a thousand necropsies on cadavers divided equally by sex,^{1d} calcification of the mitral annulus was found in 13.2 per cent of the women and 4.2 per cent of the men. The increased incidence of this disorder in women is particularly striking when the condition is contrasted with calcific aortic stenosis, for men with that disease greatly outnumber women.⁹

At the time of the first evidence of calcification the women were aged 58 to 82 (mean, 70) and the men 68 to 82 (mean, 73). Other investigators¹⁰ have more evident data showing that the disorder affects men a few years later than it does women.

Pathologic and Etiologic Aspects.—Geerling,^{1a} Giese^{1b} and Ribbert,^{1c} among other authors, have amply described the lesions with isolated calcification of the mitral annulus fibrosus; those found in our patients did not differ significantly from their descriptions. It should be noted that the mitral cusps may be thickened or even somewhat deformed near the annulus³ in the absence of mitral stenosis or other convincing evidence of rheumatic heart disease.

Two patients (cases 5 and 8) had syphilis; nothing was seen in the necropsy of 1 to indicate that syphilis had anything to do with the calcification. Arterial hypertension was frequent but usually not severe; the diastolic pressure varied from 80 to 120 mm., even in the absence of heart block.

Scars of duodenal ulcer were found at necropsies in cases 3 and 5, while those in cases 8 and 10 were discovered by radiologists in the course of examinations made because of gastrointestinal symptoms with ulcer. We know of still another case, not reported in this paper, in which death resulted from a perforated duodenal ulcer. Yet the high incidence of duodenal ulcers in our cases may be largely accidental, owing to routine fluoroscopic examinations of the chests of patients about to ingest barium sulfate.

Many pathologists consider calcification of the mitral annulus to be a process similar to that of calcific aortic stenosis. Although the lesions at these two sites are otherwise similar, it is strange that at the mitral valve the cusps are usually spared and the annulus fibrosus involved while at the aortic valve the reverse is true. Neither Sosman^{2a} nor Christian¹¹ has found isolated calcification of the supporting fibrous annulus of the aortic valve; Menezes de Oliveira³ noted its rarity.

Yet the two lesions have much in common, and since recent writers¹² favor a rheumatic origin for calcific aortic stenosis it is possible that

9. McGinn, S., and White, P. D.: Clinical Observations on Aortic Stenosis, *Am. J. M. Sc.* **188**:1-15 (July) 1934.

10. Martens,^{1d} Menezes de Oliveira.³

11. Osler,^{8b} p. 1050.

12. Hall, E. M., and Ichioaka, T.: Etiology of Calcified Nodular Aortic Stenosis, *Am. J. Path.* **16**:761-785 (Nov.) 1940.

calcification of the mitral annulus might also be rheumatic. None of our patients gave a history of rheumatic fever; none had auscultatory or roentgenologic signs of mitral stenosis (see following material), and in none of 3 cases was there evidence of rheumatic heart disease at necropsy. Gager and Pardee,¹³ on the other hand, reported a case in which the pathologic observations were suggestive of rheumatic origin.

Menezes de Oliveira³ indicated that the lesion was sometimes rheumatic; his criteria favoring this origin are: predominance on the valve leaflets, severe and multiple valvular lesions, vegetations, noncongenital fusion of valvular commissures and shortened thick chordae tendineae. Nonrheumatic calcification, on the other hand, is suggested by extensive calcification in the fibrous supporting rings (cardiac skeleton) with slight valvular lesions, or absence of such lesions and absence of other signs of endocarditis.³ Of his 100 cases, 75 fell into the latter group, which he considered to be of arteriosclerotic origin.

Atherosclerosis of the aorta was prominent. Coronary atherosclerosis was severe in case 3 but relatively slight in cases 5 and 6. Pulmonary atherosclerosis was slight in case 3 but severe in case 6 in which fibrosis of the lungs was present. Unexpected lesions were the masses of calcium in the greatly thickened intima of the large arteries of the neck in case 3. Nearly occluding these vessels, the masses may have been related causally to the postural vertigo noted by the patient in this case and to her systolic thrill and murmur. Similar, but much less pronounced, calcification in early branches of the aorta were found in case 5. It seems likely that calcification of the mitral annulus is closely related to the degenerative vascular disturbances.

Blood counts were not remarkable in any case, and routine urinalysis showed only evidence of renal arteriosclerosis. The concentrations of various substances per hundred cubic centimeters of serum in cases 2, 6 and 7, respectively, were: calcium, 9.0, 11.3 and 9.5 mg.; inorganic phosphorus as phosphate, 3.1, 4.6 and 4.1 mg.; alkaline phosphatase activity, 6.4, 5.4 and 3.7 units; cholesterol, 285, 169 and 280 mg., and protein, 8.0, 7.9 and 7.5 Gm. These results are not striking but suggest a tendency toward increased concentrations of protein and, in 2 patients, of cholesterol.¹⁴

The lesions show no evidence of progression histologically; this is what might be expected if a single massive injury or other transient cause were followed by healing with fibrosis and calcification. This

13. Gager, L. T., and Pardee, H. E. B.: Intermittent Complete Heart-Block and Ventricular Standstill, *Am. J. M. Sc.* **169**:656-662 (May) 1925.

14. Kountz, W. B.; Sonnenberg, A.; Hofstatter, L., and Wolff, G.: Blood Cholesterol Levels in Elderly Patients, in Moore, R. A.: *Ageing and Degenerative Diseases*, in *Biologica Symposia*, Lancaster, Pa., Jaques Cattell Press, 1945, pp. 79-86.

view is supported by the benign clinical course observed in cases 7 and 10. On the other hand, calcification noted during October 1945 in case 4 was not seen, in spite of careful specific search fifteen months earlier; increasing calcification was observed in 1 patient over a nine year period.¹⁵

Heart Block.—Geerling's^{1a} anatomic studies show that the portion of the mitral annulus fibrosus which lies in the interventricular septum is the least commonly calcified. Heart block may be expected when calcification extends into the septum, particularly when excrescences reach out from the ring to invade the conducting system more deeply; such localization may be as much a matter of chance as a question of degree of the lesion. Geerling^{1a} and Ritchie⁵ presented roentgenograms of two hearts taken after the deaths of patients in whom heart block had been present, and there was a prolonged conduction time in 1 of Saul's¹⁶ patients, but apparently disturbances of conduction are rare.³

In at least 3 of the 4 cases with necropsy, reported by Comeau¹⁷ as instances of paroxysmal complete heart block, calcification played a major part. Starling's patient with block, which was induced by swallowing and prevented by atropine, later was subject to permanent complete heart block, and at necropsy a calcareous lesion was described by T. Lewis.¹⁸ With this background it is not surprising that of our 5 patients with complete heart block, sinus rhythm with normal conduction times reappeared temporarily in 2 (cases 1 and 5); the transient complete block in case 2 was probably related to digitalis.

We have not attempted to demonstrate the precise nature of the lesions located in the conducting system at necropsy, and it is quite possible that calcification was not the direct cause of block. In case 4, for example, calcification was not found for eight years after the discovery of complete heart block but was eventually seen after another year. As recently suggested,¹⁹ transient ischemia of the nodal region might also be considered responsible for paroxysmal block.

The apical auricular murmur was never heard when auriculoventricular conduction was normal (see following material).

15. Odqvist, H.: Studien über den Röntgenbefund bei intrakardialen, speziell perimitralen Verkalkungen, *Acta radiol.* **25**:686-700 (Nov.) 1944.

16. Saul, W.: Verdichtungen im Herzschatten, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **46**:450-457 (Oct.) 1932.

17. Comeau, W. J.: Paroxysmal Complete Heart Block Alternating with Normal Rhythm and Conduction, *Am. J. M. Sc.* **194**:43-53 (July) 1937.

18. Lewis, T.: Postmortem Notes of Dr. J. H. Starling's Case of Heart-Block, *Heart* **9**:283-287 (Dec.) 1922.

19. Roos, A.: Paroxysmal Complete Heart Block, Produced by Ischemia of the Auriculoventricular Node, *Am. Heart J.* **30**:238-252 (Sept.) 1945.

Murmurs.—A loud, rough murmur accompanied ventricular systole in cases 1 to 3 and 5 to 7, was moderate in case 10 but was not prominent in cases 4, 8 and 9. It was usually most intense at the base and along the left sternal border from the second to the fifth interspace, but it was heard also at the apex in cases 1 to 6 and 10 and over the carotid artery in cases 1 and 3. There was an associated thrill in case 3 only.

Mitral regurgitation is a commonly given explanation for a systolic murmur confined to the apex but is hardly satisfactory when the apical murmur is even louder at the aortic area as in the present cases.²⁰ The left auricle was never found to be dilated (except with congestion and auricular fibrillation in case 2 and after a lapse of time in case 4), and it is difficult to imagine the dilatation of a valve ring which has first become heavily calcified. The heart as a whole was not enlarged in cases 7, 8 and 10, slightly enlarged in cases 1 (temporarily) 2 and 9 and moderately or greatly enlarged in cases 3, 4, 5 and 6; there was no more than a rough correlation, with several exceptions, between cardiac dilatation and the intensity of the systolic murmur. With no other apparent change the murmur first appeared in case 7 long after the calcific lesion was noted.

Although the second heart sound was normal in all patients, calcific aortic stenosis was sometimes suspected; it was not present in any of the necropsies. The masses of calcium found in the aortic branches in case 3 may have been the cause not only of the murmur but also of the thrill and attacks of postural dizziness noted in that patient. The degree of aortic or pulmonary atherosclerosis and dilatation may have been enough in all cases to account for the murmur with ventricular systole. The murmur of aortic insufficiency was heard in case 9.

Libman⁷ has suspected the presence of calcification of the mitral ring on hearing a systolic murmur along the left sternal border but not in the aortic area; his description is applicable only in cases 7 and 8, so that the diagnostic value of such a murmur is not convincing. We have been unable to find a satisfactory case report describing the signs of mitral stenosis with calcification of the mitral annulus fibrosus. Cohen, Gray, Nash and Fink²¹ wrote of a presystolic murmur in their case 2, but calcification was neither seen roentgenologically nor noted at necropsy. Menezes de Oliveira³ found questionable diastolic murmurs in only 2 of 75 patients with "arteriosclerotic" calcification of the mitral annulus. In necropsies of 11 such patients, he found

20. Baker, L. A.; Sprague, H. B., and White, P. D.: The Clinical Significance of Loud Aortic and Apical Systolic Heart Murmurs Without Diastolic Murmurs, *Am. J. M. Sc.* **206**:31-43 (July) 1943.

21. Cohen, L.; Gray, I.; Nash, P. I., and Fink, H.: Calcareous Aortic Stenosis: Report of Nine Cases with Autopsy Findings, *Ann. Int. Med.* **13**: 2091-2103 (May) 1940.

slight mitral stenosis once and questionable mitral regurgitation once; otherwise there were no mitral abnormalities of functional importance and no left auricular dilatation.²² In only 1 case did he judge the calcareous lesion to be the sole cause of a loud systolic murmur. In none of our patients with normal conduction time was there an apical murmur during ventricular diastole. On the other hand, a blowing murmur restricted to the apex during this part of the cardiac cycle was audible in the 4 ambulatory patients (cases 1 to 4) of the 5 with heart block. Records of the heart sounds not only confirmed the presence of an actual murmur, as distinguished from the auricular sounds which often accompany heart block, but showed it to be related to auricular activity. When this even took place early in ventricular diastole, the murmur was loudest; later it was less intense. These changes were easily detected on auscultation. As noted, the murmur was present in early diastole during a period of auricular fibrillation in cases 1 and 2; otherwise, the murmur never occurred during the period of rapid ventricular filling unless auricular activity coincided.

In some cases of heart block phonocardiograms have revealed prolonged sound vibrations associated with auricular activity,²³ but apparently these have not been interpreted as murmurs clinically. However, Wolferth and Margolies²⁴ and Stead and Kunkel²⁵ have reported on 2 patients (case 1 in each paper) with heart block and an auricular murmur appreciated as such on auscultation. We have phonocardiograms which confirm clinical observations that an apical murmur was present during ventricular diastole in 5 more elderly patients with conduction defects. Their cases are not reported in this paper because no calcification could be detected roentgenologically in spite of careful search, but it is of interest that case 4 was at first included with them.

Mechanisms which might be involved in the production of the auricular murmur will be discussed more completely elsewhere, but several points may be mentioned here. The murmur is not directly related to the calcareous lesion but does seem to be related to heart block; found in our patients only when block also occurred, it was absent even in them whenever the P-R interval happened to fall within the normal range, as in the first cycle of figure 2. Measurements of

22. These facts are not correctly cited in the book review.³

23. Orias, O., and Braun-Menéndez, E.: *The Heart-Sounds in Normal and Pathological Conditions*, London, Oxford University Press, 1939, p. 111.

24. Wolferth, C. C., and Margolies, A.: *The Influence of Auricular Contraction on the First Heart Sound and the Radial Pulse*, *Arch. Int. Med.* **46**:1048-1071 (Dec.) 1930.

25. Stead, E. A., Jr., and Kunkel, P.: *Factors Influencing the Auricular Murmur and the Intensity of the First Heart Sound*, *Am. Heart J.* **18**:261-270 (Sept.) 1939.

its time relationships further suggest that it does not occur with, but rather follows, auricular systole. Such behavior is quite unlike that of the presystolic murmur of rheumatic mitral stenosis, and there is neither pathologic nor roentgenologic evidence of obstruction to flow through the mitral orifice by calcification of its annulus fibrosus as a general rule.

Fibrosis of the mitral leaflets is a common occurrence in the aged; this, either alone or with the addition of calcification extending from the annulus fibrosus into the proximal portions of the cusps as in cases 3 and 5, need not obstruct the flow but might modify the usual movements of the leaflets which follow auricular systole. In the absence of conduction defects, no physical signs would appear. But with delayed ventricular systole, the thickened leaflets might conceivably permit reflux of blood into the auricle or might vibrate in the stream as ventricular filling continues; a murmur such as was found in our patients could be the result in either case.

Roentgenologic Aspects.—Several observers²⁶ have described the roentgenologic aspects of calcification of the mitral annulus fibrosus, differentiating this from the calcific lesions in the valve leaflets of patients with rheumatic mitral stenosis. Prominence of the left auricle is rarely found.

In a roentgenkymographic study, Sundberg²⁶ calculated that six sevenths of the stroke volume is due to descent of the base of the heart toward the apex during systole. Roentgenkymograms in cases 2, 6, 7 and 9 all show this movement to be much more striking than the lateral motion of the walls (fig. 7), another bit of evidence confirming the opinion²⁷ that estimates of cardiac output based on roentgenkymography are not trustworthy.

Cardiac Symptoms.—Congestive heart failure occurred in 5 patients (cases 1, 2, 3, 5 and 6). Of these, heart block was present in all but the last. Congestion was not apparent in cases 4 and 7 to 10. Angina pectoris was surprisingly rare, occurring only in cases 2 and 3; myocardial infarction was found in the latter. Only 1 patient (case 5) had the Stokes-Adams syndrome. Cardiac symptoms seem to be even less common in cases reported by others; this is especially noteworthy when one recalls the age incidence of this disorder. We know of 1 other patient, not included in this report, in whom necropsy showed acute bacterial endocarditis as a complication.

With such a relative paucity of associated cardiac symptoms, it should not be surprising that in so many patients the calcific lesion is found by chance.

26. Footnote 2. Menezes de Oliveira.³

27. Hamilton, W. F.: Notes on the Development of the Physiology of Cardiac Output, Federation Proc. 4:183-195 (June) 1945.

Prognosis.—Prognosis seems to be determined chiefly by the occurrence of heart block. Of the patients with block, those in cases 1, 2 and 3 died five, two and three years after the discovery of their lesions, and the one in case 5 died within a year of the onset of cardiac symptoms; the patient in case 4, on the other hand, is still living and ambulatory nine years after the onset of heart block. Without defective conduction the patient in case 6 died in six years but those in cases 7 to 10 are alive after one, three, eight and eleven years. The causes of death were cerebral vascular disease in case 1, myocardial infarction in case 3 and congestive heart failure in cases 2, 5 and 6.

It is most interesting that in case 7 the patient is alive and well as far as her heart is concerned, eleven years after the lesion was found. Likewise in case 10 the patient has no cardiac symptoms after eight years. The only apparent change in them was the development of a systolic murmur in the former; specifically, there was neither lengthening of conduction time nor change in the roentgenologic appearance. The clinical course in these cases suggests that calcification of the mitral ring is at the most a slowly progressive disorder after the initial damage has occurred.

Clinical Diagnosis.—After observing case 1, we ventured the diagnosis of calcification of the mitral annulus fibrosus in cases 2, 3 and 4 on finding complete heart block and an apical diastolic murmur in each of the elderly patients. The diagnoses were confirmed roentgenologically, even though digitalis played a part in the block in case 2 and only after a delay of three years in case 4.

On the other hand, the same diagnosis was not confirmed roentgenologically in 5 other elderly patients with identical cardiac signs. Whether calcification will eventually appear in them, as in case 4, is a question that must be left to the future; it is strongly suspected that noncalcific degenerative lesions are adequate to produce the syndrome.

SUMMARY

Clinical observations are recorded concerning 10 patients with calcification of the mitral annulus fibrosus.

The ages of the patients range from 58 to 82; 7 were women.

None had a history of rheumatic fever, and there was no convincing evidence of rheumatic heart disease in three necropsies. Atherosclerosis was marked; calcification of the large arteries to the neck was found at two of the necropsies.

Congestive heart failure occurred in 5 patients, angina pectoris in 2 only. Arterial hypertension was present in practically every case but was not often severe.

Five patients had complete heart block. This was paroxysmal in 2, while partial block in a third was temporarily made complete by digitalis. Four of these patients, but only 1 of those without block, have died.

In 7 patients there was a moderate or a loud, rough murmur with ventricular systole.

In the 4 ambulatory patients of the 5 with heart block there was a blowing apical murmur, related to auricular activity, during ventricular diastole; auricular sounds of uncertain nature were recorded for the fifth. This murmur did not occur in the patients with normal auriculo-ventricular conduction but it has been noted in other elderly patients with heart block and without roentgenologic evidence of calcification.

The significance of the murmurs is not clear, but they were not regarded as evidence either of mitral regurgitation or of mitral stenosis.

Two patients were observed again a decade after the discovery of their calcific lesions; no significant changes were found other than the appearance, in 1, of a systolic murmur. With regard to a third patient diligent roentgenologic study failed to demonstrate calcification eight years after the onset of complete heart block, but it was successful after one more year.

Calcification of the mitral annulus fibrosus may be suspected in elderly persons after the finding of heart block and an apical murmur associated with auricular activity during ventricular diastole.

ERYSIPELOTHRIX RHUSIOPATHIAE INFECTION IN MAN

Report of a Case with Cutaneous Bullae, in Which Cure Was
Achieved with Penicillin

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THE numerous cases, which have been reported, of infection of human beings by *Erysipelothrix rhusiopathiae*, the causative agent of swine erysipelas, fall into three rather well defined clinical categories (see Klauder¹ for the literature). These are (1) a mild, localized cutaneous form (erysipeloid of Rosenbach²), (2) a severe, generalized cutaneous form and (3) a septicemic form, with or without cutaneous involvement, sometimes complicated by specific endocarditis (Russell and Lamb³). The less frequent clinical and anatomic manifestations which have been recorded are arthritis (Düttmann,⁴ Brind⁵ and Wüthrich⁶), meningitis (Dumont and Cotoni⁷), lymphangitis and lymphadenopathy (Schölzke⁸), optic neuritis (Peters⁹), intracranial abscess (Torkildsen¹⁰) and osseous necrosis (Klauder, Kramer and Nicholas¹¹).

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From the Army Institute of Pathology, Army Medical Museum, Washington, D. C.

1. Klauder, J. V.: *Erysipelothrix Rhusiopathiae* Infection in Swine and in Human Beings, *Arch. Dermat. & Syph.* **50**:151-159 (Sept.) 1944.

2. Rosenbach: Ueber das Erysipeloid, *Arch. f. klin. Chir.* **36**:346-350, 1887.

3. Russell, W. O., and Lamb, M. E.: *Erysipelothrix* Endocarditis, *J.A.M.A.* **114**:1045-1050 (March 23) 1940.

4. Düttmann, G.: Schweinerotlauf und Erysipeloid, *Beitr. z. klin. Chir.* **123**:461-470, 1921.

5. Brind, A. I.: Arthritis of Erysipeloid Etiology, *Novy khir. arkhiv.* **47**:177-181, 1940.

6. Wüthrich, A.: Die chronische Erysipeloidarthritis mit röntgenologisch sichtbaren Knochenzerstörungsvorgängen, *Beitr. z. klin. Chir.* **174**:98-103, 1942.

7. Dumont, J., and Cotoni, L.: Bacille semblable au bacille du rouget du porc rencontré dans le liquide céphalo-rachidien d'un méningitique, *Ann. Inst. Pasteur.* **35**:625-633, 1921.

8. Schölzke, K. H.: Seltener klinischer Verlauf eines Erysipelds, *Med. Klin.* **33**:1299-1300, 1937.

9. Peters: Personal communication; cited by Callomon.¹²

10. Torkildsen, A.: Intracranial Erysipeloid (Swine-Erysipelas) Abscess: A Variety of Abscess Not Hitherto Observed, *Bull. Hyg.* **18**:1013, 1943; abstracted, *Acta chir. Scandinav.* **89**:89-96, 1943.

11. Klauder, J. V.; Kramer, D. W., and Nicholas, L.: *Erysipelothrix Rhusiopathiae* Septicemia: Diagnosis and Treatment, *J. A. M. A.* **122**:938-943 (July 31) 1943.

Characteristically, the cutaneous lesions assume the form of superficial, more or less circumscribed, slightly elevated and moderately edematous areas of erythema (Callomon¹²). Vesication of the eruption has been but rarely observed and then chiefly in the form of hemorrhagic blebs at the site of inoculation (Klauder¹). In the case reported in this paper bullous vesication was an outstanding feature and engendered considerable diagnostic difficulty and therapeutic delay because it has not heretofore been recognized that erysipeloithrix infection in man may assume this form.

Intensive therapy with penicillin was instituted because of the results reported by Heilman and Herrell,¹³ who found this antibiotic substance highly potent in the treatment of experimental infection of mice. The rapid and complete clinical cure which resulted indicates that penicillin therapy is more effective in the treatment of this disease than the use of specific antiserum or of sulfonamide compounds (Klauder and Rule¹⁴), cryotherapy (Griswold and Bowen¹⁵) or ultraviolet irradiation (Mühlpfordt¹⁶).

REPORT OF CASE

J. A. H., a 46 year old white farmer, was admitted to the Eugene Leland Memorial Hospital, Riverdale, Md., on Jan. 20, 1945 (service of Dr. Wendell E. Malin, Riverdale, Md.). Four days before admission he had slaughtered and dressed a "sick" hog. The following day he noticed a red, swollen, tender area on his right hand in the vicinity of an abrasion which had been present before the slaughter. The redness and swelling extended rapidly and by the next day had reached the elbow. Numerous vesicles formed, and there was intense itching of the involved skin; the patient and his family physician thought that he had "poison ivy." Sulfonamide compounds were administered, and wet dressings were applied, without benefit. On the fourth day lesions appeared on the neck, the face, the ears (fig. 1) and the left hand (fig. 4 C); there was stiffness as well as pain in the right shoulder, and the patient felt feverish and ill. By the time he entered the hospital that evening large bullae were present on the hands and the right arm; areas of redness were present on the face and the neck, and the eyes were closed by edema of the eyelids (fig. 1). The patient had lapsed into stupor.

12. Callomon, F.: Pseudoerysipel, Erysipeloid, in Jadassohn, J.: *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1929, vol. 9, pt. 1, pp. 93-124.

13. Heilman, F. R., and Herrell, W. E.: Penicillin in Treatment of Experimental Infections Due to Erysipelothrix Rhusiopathiae, *Proc. Staff Meet., Mayo Clin.* **19**:340-345, 1944.

14. Klauder, J. V., and Rule, A. M.: Sulfonamide Compounds in Treatment of Erysipelothrix Rhusiopathiae Infections, *Arch. Dermat. & Syph.* **49**:27-32 (Jan.) 1944.

15. Griswold, C. M., and Bowen, S. S.: Treatment of Erysipeloid by Cryotherapy, *Arch. Dermat. & Syph.* **49**:348-350 (May). 1944.

16. Mühlpfordt, H.: Rotlaufserumbehandlung oder Höhensonnenintensivbestrahlung des Erysipeloids? *Dermat. Ztschr.* **60**:445-450, 1931.

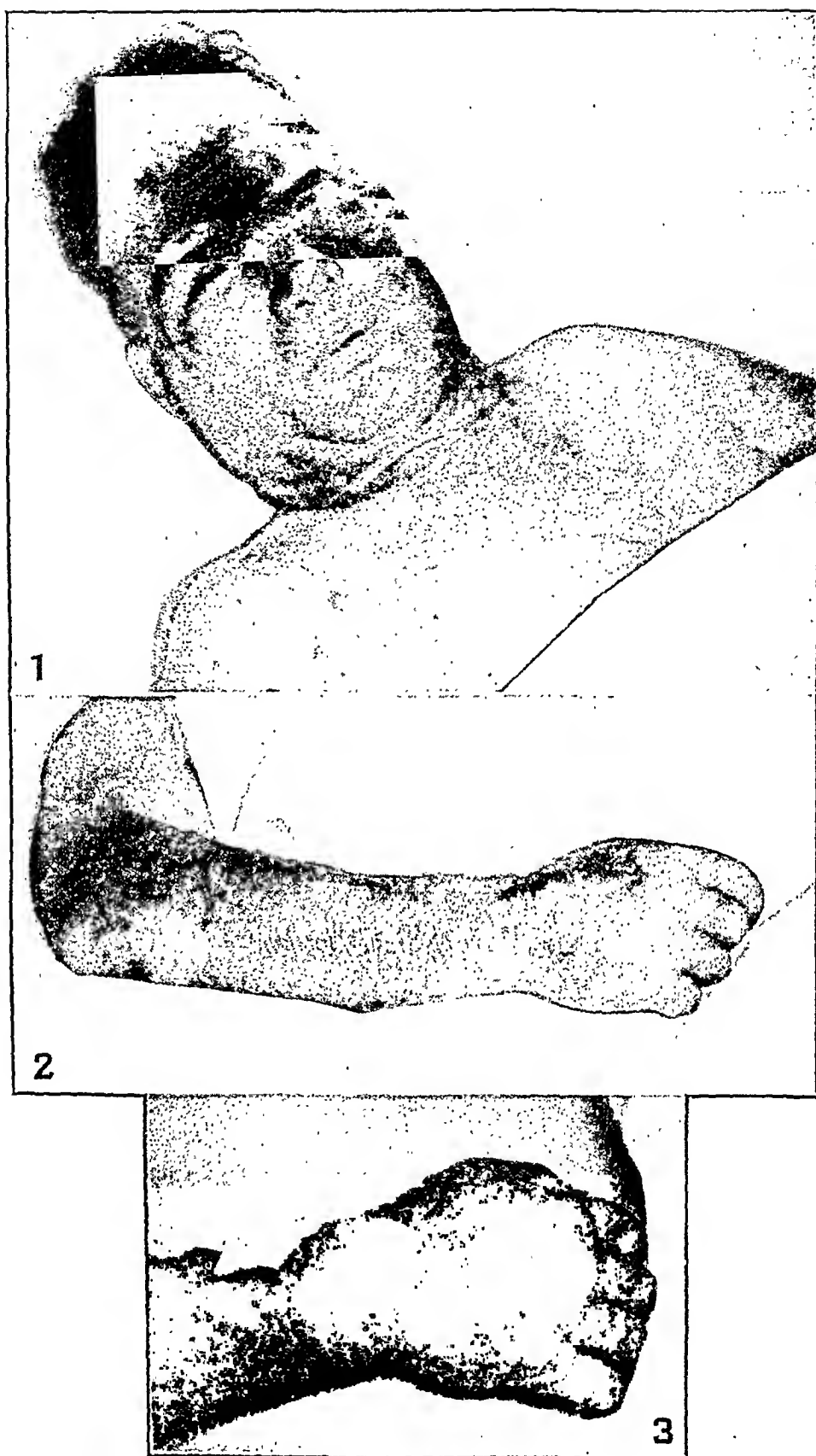


Fig. 1.—*Erysipelothrix rhusiopathiae* infection in a 46 year old white man.

Additional information, which proved to be of considerable importance, was elicited later. It was learned that three weeks prior to the onset of the present episode he had had several painful reddish lesions on his right hand. These had healed slowly and had almost disappeared at the time he slaughtered the hog, four days before his admission to the hospital.

Examination.—When the patient was admitted to the hospital, his temperature was 98.4 F.; the respirations were 20 and the pulse beats 80 per minute and the blood pressure was 180 systolic and 90 diastolic. The significant features on physical examination were limited to the skin. Eruptions were present on both of the upper extremities, the face, the ears, the neck, the shoulders and the sternum; the changes were most extensive on the right hand and forearm. A traumatic abrasion, about 1 cm. in diameter, on the dorsum of the right hand was apparently the site of inoculation; it was covered with a black crust and surrounded by a wide zone of intense redness and edema. The right hand and forearm were studded with huge bullae, which appeared, in areas, to have coalesced. The surface was tense, shiny and bluish purple, and the contents were clear. The intervening skin was diffusely erythematous, and there was no sharp transition to normal integument. A few bullae were present on the left

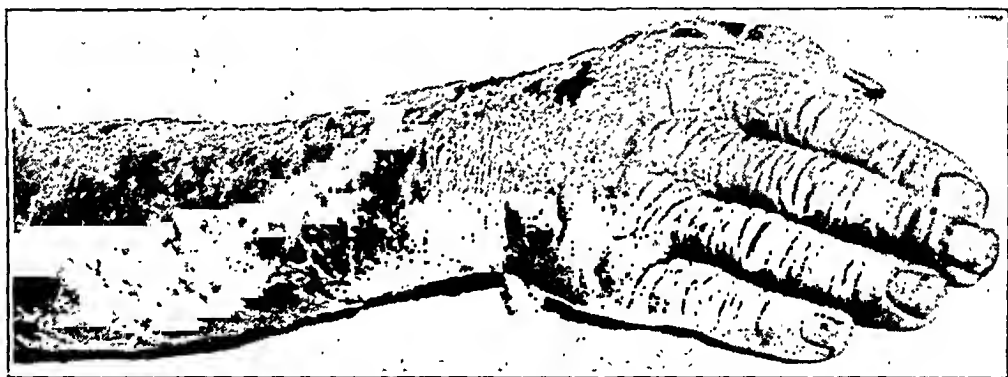


Fig. 2.—Appearance of right hand and arm fourteen days after the patient's admission to the hospital. They show exfoliation of large sheets of tissue.

hand and forearm (fig. 4 C). The lesions on the face, the neck and the shoulders were of an entirely different character; they were sharply circumscribed, slightly raised and indurated plaques (fig. 1), which were bright red at the periphery and purplish in the center. Ill defined areas of erythema were observed on the chest and the back at this time, but there were no discrete lesions.

Laboratory Data.—During the first week, blood counts revealed 12,000 to 15,000 leukocytes per cubic millimeter, with 85 per cent polymorphonuclear leukocytes. On one occasion, 4 per cent eosinophils was reported; otherwise, the differential count was normal. Several urinalyses disclosed no significant abnormalities. On January 20 examination showed 6.1 mg. of the sulfonamide compound per hundred cubic centimeters of blood; on January 26 the total chlorides were 570 mg.

A direct smear of the contents of a bleb revealed a few gram-positive cocci, resembling staphylococci. Cultures on plain broth, Loeffler's agar and blood agar yielded *Staphylococcus* (type not stated), which was thought to be a contaminant. Culture of blood taken on the day after the patient's admission to the hospital was negative for staphylococci, but the procedure was not carried

out under optimal conditions. Culture of a second sample, obtained after penicillin therapy was well under way, and of a fragment of exfoliated skin, was also negative for staphylococci.

The Wassermann test of the blood and agglutination tests for typhoid, paratyphoid, undulant fever and tularemia were negative. Two samples of serum, obtained on the fifth and fourteenth days after the patient's admission to the hospital, were submitted for agglutination tests for *Erysipelothrix* to the Pathological Division of the Bureau of Animal Industry, United States Department of Agriculture. The report read in part: "Agglutination tests were conducted on the two samples of serum. The first reacted at 1:200 dilution with swine erysipelas tube antigen and very rapidly with the plate antigen. The second sample of serum failed to agglutinate plate antigen when it was tested in the usual manner. On dilution of the serum with saline solution, a fine clumping of the plate antigen was noted. This second sample of serum agglutinated tube antigen at 1:25 did not react at 1:50 and 1:100 but reacted strongly at 1:250 and 1:1,000." Agglutination tests on a third sample of serum, taken three weeks after the patient was discharged from the hospital, gave negative results.

The Pathological Division of the Bureau of Animal Industry of the United States Department of Agriculture and the Maryland Livestock Sanitary Board were instrumental in recovering for study a portion of the carcass of the hog which had been slaughtered by the patient. Typical rhomboid cutaneous lesions were present, and agglutinations were positive for swine erysipelas. *Ery. rhusiopathiae* grew on culture of the skin and of material from the joints of the hog. Additional members of the herd to which this hog, belonged were found to be infected.

Course.—Penicillin therapy was initiated at the time of the patient's admission to the hospital at an arbitrary dose of 20,000 units, administered intramuscularly every three hours. This appeared to bring about slight improvement and to arrest the fulminant progress of the disease, but when the diagnosis was definitely established the quantity was increased to 40,000 units every three hours. Twenty-four hours later the patient emerged from his stupor. During the succeeding days there was a dramatic clinical improvement. The temperature, which had fluctuated between 102 and 104 F., and the pulse rate, which had ranged between 100 and 130, rapidly returned to normal. About fifteen days after his admission to the hospital it was necessary to interrupt the administration of penicillin; fever and constitutional symptoms recurred but cleared promptly when therapy was resumed.

The erythema of the upper extremities spread rapidly to the shoulders, the neck and the face. By the end of the first week these regions had become intensely violaceous, in striking contrast to the uninvolved areas (fig. 3A). During the first few days large irregular erythematous discolorations developed on the back (fig. 3B). The erythema remained after regression and exfoliation of the bullae and plaques were complete; a significant flush on the face and the upper extremities persisted for several weeks after the patient was discharged.

The bullous lesions of the hands and the arms progressively enlarged, sometimes by coalescence, and after they remained stationary in size for a varying period their fluid contents were absorbed. None of the lesions suppurated. The thick layers of dried, loosened skin which remained were ultimately desquamated (figs. 2 and 4, D and E). Some of the exfoliated tissue came off in large sheets, and that over the hands could be pulled off like parts of a glove. These changes

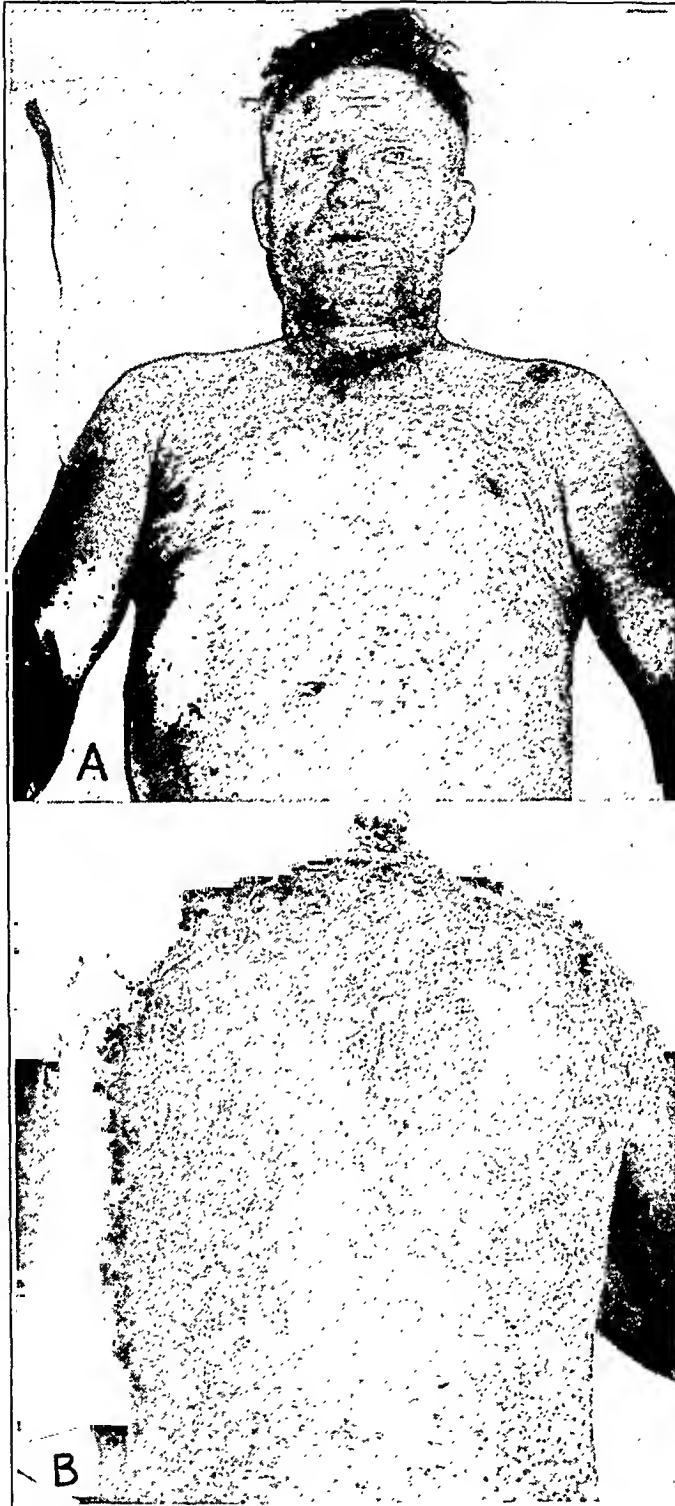


Fig. 3.—*A*, appearance of the patient fourteen days after his admission to the hospital. He has recovered from his stupor. There is marked reduction in the edema of the face and neck. Note the deep erythema of the arms, the shoulders, the neck and the face and the crops of fresh lesions on the chest. *B*, appearance of the patient's back fourteen days after his admission to the hospital. There are older confluent and recent discrete lesions on the back with patchy scaling.

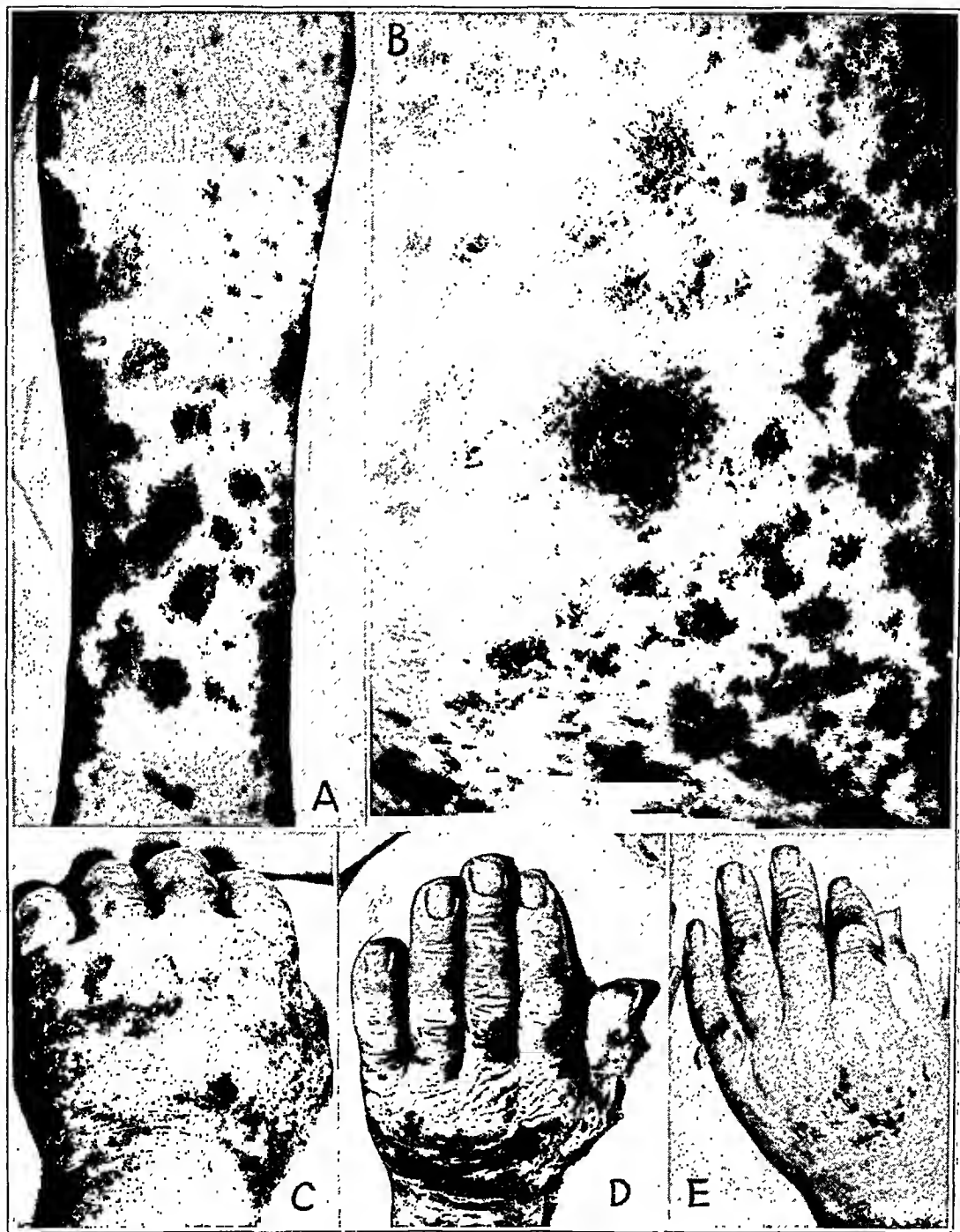


Fig. 4.—*A*, eruptions fourteen days after the patient's admission to the hospital. There are circumscribed erythematous plaques on the legs reminiscent of "diamond skin" lesions in swine. *B*, fresh crop of lesions on the chest fourteen days after the patient's admission to the hospital. They consist of red papules occurring in groups. *C*, *D* and *E*, the left hand on the fifth, the fourteenth and the thirty-first day, respectively. The huge bleb in *C* is dried and loosened in *D* and almost completely desquamated in *E*.

recalled the extensive sloughing which sometimes occurs in the hog (Stiles and Davis¹⁷).

The flat circumscribed lesions present on the neck and the shoulders at the time of the patient's admission to the hospital continued to appear in crops on the chest (fig. 4 *B*), in the axillas and on the abdomen and the legs. They began as clusters of papules which coalesced to form circumscribed plaques. On the legs, their appearance was somewhat reminiscent of the so-called "diamond skin" or "urticarial" patches of the hog (fig. 4 *A*). Lesions of this type never vesicated. They turned purple, and the color faded from the center outward; these changes were associated with a moderate degree of scaling in striking contrast to the exfoliation of thick layers of tissue in the areas of vesication.

The evolution of the cutaneous lesions was accelerated, and the edema of the face and the neck, which had profoundly altered the patient's appearance,



Fig. 5.—General appearance of the patient thirty-one days after his admission to the hospital.

receded rapidly after the dose of penicillin was increased (fig. 5). The patient was discharged from the hospital six weeks after his admission, completely recovered. At present, ten months after his illness, he shows no evidence of chronic infection or complications.

Histologic Observations.—The first specimen was taken from a bleb on the left hand three days after the patient's admission to the hospital (fig. 6, *A* and *B*). It was evident that the vesication had occurred in the stratum germinativum of the epidermis. Intracellular and intercellular edema involved groups of cells in this layer in areas where cavitation had not as yet occurred. Small vesicles,

17. Stiles, G. W., and Davis, C. L.: Swine Erysipelas and Its Economic Importance, J. Am. Vet. M. A. 84:895-906, 1934.

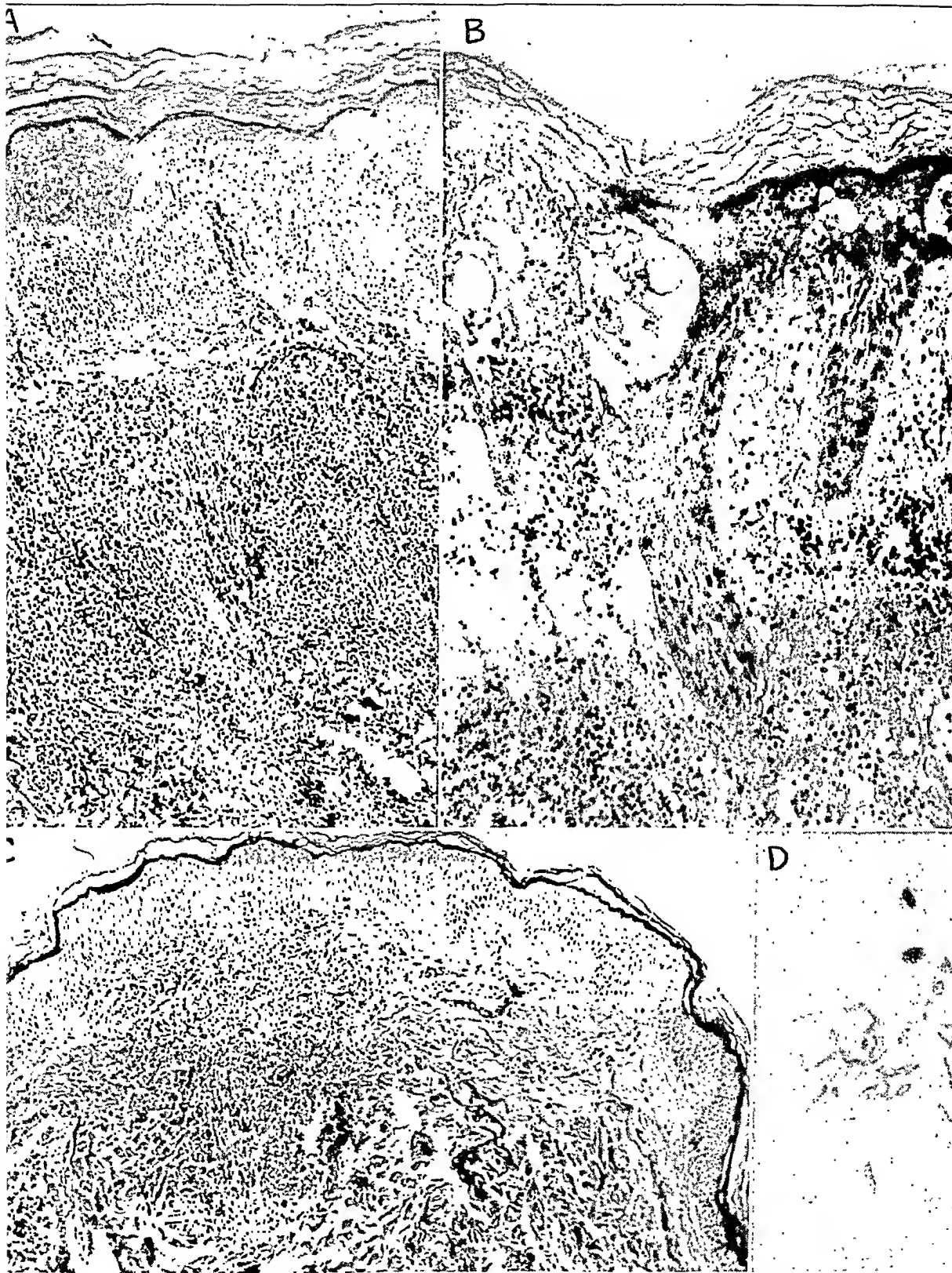


Figure 6

(See legends on opposite page)

whose diameters corresponded to those of two or three prickly cells, were numerous and sometimes occurred in groups which had partially fused (fig. 6 *B*). The largest cavities, which had evidently formed by coalescence, were covered with a few layers of cells belonging to the stratum germinativum, the stratum granulosum and the stratum corneum. On the side of the dermis there remained a thinned-out layer of basal cells which in some areas was broken through, allowing the bleb to communicate with the edematous papillary layer of the cutis. In some areas the surface layers of cells were necrotic. In one section, balloon degeneration of prickly cells and cavitation by reticular collimation were evident.

The bullae contained serum, fibrin, erythrocytes, polymorphonuclear leukocytes, epithelial cells in various stages of degeneration and nuclear debris. Similar constituents were present in some of the smaller vesicles. Occasionally, dense collections of polymorphonuclear leukocytes gave the impression of early formation of pustules. In one section a few of these were located just beneath the stratum lucidum.

The epidermal pegs were elongated and in some areas were separated by edematous and clubbed papillae of the dermis. Numerous polymorphonuclear leukocytes were margined along the dermoepidermal junction; some of the pegs were invaded by these cells as well as by occasional lymphocytes. A severe degree of serohemorrhagic edema was present in the papillary zone of the cutis. In this region the capillaries were extremely dilated and engorged with erythrocytes. Interfibrillar accumulations of serum and fibrin and areas of hemorrhage were present. The dermal collagen was swollen, and there was some loss of fibrillar markings. The lymph vessels were moderately dilated and appeared empty. Cellular infiltration of this region was relatively slight and consisted of scattered polymorphonuclear leukocytes and occasional eosinophils. Elastic fibers stained poorly and appeared frayed out.

The infiltrate was concentrated just below the papillary layer of the cutis and was composed of polymorphonuclear leukocytes and eosinophils. In some areas, nodular collections of polymorphonuclear leukocytes were so dense as to suggest early abscess formation. The blood vessels in this layer were filled with polymorphonuclear leukocytes; here, too, the collagenic fibers were noticeably swollen. The inflammation extended, particularly around the blood vessels and the sweat glands, through the cutis to its junction with the panniculus. At the edge of the lesion, there was a gradual transition to normal skin.

EXPLANATION OF PLATE.

Fig. 6.—*A*, low power view of the epidermis and the upper part of the cutis in the first specimen. Note the intercellular and intracellular edema in the stratum germinativum, the severe edema and the capillary engorgement in the papillary layer of the cutis and the infiltrate concentrated in the subpapillary layer and the zona reticularis. $\times 100$. *B*, higher power view of first specimen. The epidermis shows various stages of vesication. Note the smaller cavities to the right and the large cavity to the left, which has ruptured through the basal layer into the edematous dermis. Serum, fibrin, degenerated epithelial cells and polymorphonuclear leukocytes may be seen in the spaces. Note the intercellular edema in the pegs, the edema and clubbing of the papillae and the severe edema and hemorrhage in the cutis. $\times 200$. *C*, low power view of second specimen. Note the widening of the epidermis, the moderate perivascular collections of lymphocytes and the wedge-shaped dense infiltrate reaching to the epidermis. $\times 100$. *D*, detail of the second specimen. A group of *Ery. rhusiopathiae* is seen in the center of the lesion illustrated in *C*. $\times 2,700$.

No bacteria were found in sections stained by the Giemsa, Warthin-Starry, Ziehl-Neelsen and Brown and Brenn methods. Mast cells were not significantly increased.

The second specimen was excised on the eighteenth day of illness from a flat plaque on the chest. The histologic changes were less severe than those in the previous sections (fig. 6C). The epidermis was widened and lightly infiltrated by polymorphonuclear leukocytes and lymphocytes. Intracellular and intercellular edema was present but to a lesser degree than in the first specimen. There was no histologic evidence of vesicle formation.

Moderate numbers of lymphocytes were distributed around the blood vessels of the subpapillary layer of the cutis. In addition, a wedge-shaped and rather sharply delimited collection of polymorphonuclear leukocytes was present. It extended from the middle of the cutis to the basal layer of the epidermis and suggested an early focus of suppuration, possibly of embolic origin. Stains for bacteria revealed a cluster of gram-positive organisms with the characteristic appearance of *Ery. rhusiopathiae* in the center of this lesion (fig. 6D).

COMMENT

The diagnosis of erysipelothrix infection was established by the rising titers of agglutinins in the patient's serum and by the presence of characteristic bacteria in sections of a cutaneous lesion. Although efforts to recover the organisms from samples of blood and fragments of exfoliated skin failed, cultures of the skin and of material taken from the joints of the hog responsible for the infection yielded *Ery. rhusiopathiae*. It appears likely that at one time infection of the blood stream existed, since widespread dissemination of the eruption in this disease is often associated with sepsis and the histologic characteristics of one lesion suggested an embolic origin.

The bullous character of the eruption which distinguished the early stage is decidedly unusual (Callomon¹² and Nékám¹⁸). In the literature the scattered references to vesiculation allude chiefly to the formation of hemorrhagic blebs at the site of inoculation (Klauder¹), although in a few instances formation of vesicles has been observed in man (Düttmann,⁴ Veilchenblau,¹⁹ Arnholz²⁰ and Sieben²¹) and in swine (Hutyra, Marek and Manninger²²).

18. Nékám, L.: *Corpus Iconum Morborum Cutaneorum*, Leipzig, Johann Ambrosius Barth, 1938, vol. 5, pt. 3, pp. 4402 and 4410.

19. Veilchenblau, L.: Zur Uebertragung des Schweinerotlaufs auf den Menschen, *Deutsche med. Wchnschr.* **47**:1030-1031, 1921.

20. Arnholz, F.: Zur Pathologie und Therapie des Erysipeloids, *Arch. f. klin. Chir.* **135**:736-750, 1925.

21. Sieben, H.: Generalisierter Schweinerotlauf beim Menschen, *Med. Klin.* **21**:129-130, 1925.

22. Hutyra, F.; Marek, J., and Manninger, R.: *Special Pathology and Therapeutics of the Diseases of Domestic Animals*, Chicago, Alexander Eger, 1938, vol. 1, p. 84.

The bullae produced a picture reminiscent of pemphigus vulgaris (Nékám,¹⁸ illustration no. 2796) and dermatitis venenata. The intense pruritus associated with the blebs, their rapid spread, the infiltrate with numerous eosinophils, the capillary engorgement and the swelling of collagen suggest that hyperergy may have played a role in the exceptional course which the infection pursued.

The importance of the imperfectly understood allergic phenomena in erysipelothrux infection has been recognized by many observers (Callomon¹²). Belgodere²³ suggested that "erysipeloid may perhaps appear only in those persons who, by reason of their profession, have already been subjected to previous contacts, as a result of which they have become sensitized." Accidents ascribable to anaphylaxis are frequent during vaccination of animals (Monnier²⁴). Curious immediate and delayed reactions in the vicinity of the site of an injection of immune serum have been observed (Callomon¹²).

Precipitins (Ascoli²⁵) and agglutinins (Schoening, Creech and Grey²⁶), have been described. Jadassohn and Mu²⁷ referred to a bacterial product, erysipeloidin, which retains some of the antigenic properties of the whole organism. In the case reported in this paper and in the cases reported by Schoening and Creech²⁸ and Ingram and Stuart²⁹ the titer of agglutinins reached 1 to 1,000 at the height of the illness and returned to 0 several weeks after recovery. Bierbaum and Gottron³⁰ reported normal titers of agglutinins in cases of the mild, localized form. Erysipelothrux infection does not confer lasting immunity; infection may readily occur again (Biberstein³¹).

23. Belgodere, G.: Supplément à l'histoire de l'érysipéloïde (inoculation à l'homme du bacille du rouget du porc), *Ann. de dermat. et syph.* **6**:193-228, 1935.

24. Monnier, J. C. E. H.: *Le rouget humain*, Thesis, Paris, 1935, pp. 1-110.

25. Ascoli, A.: Die Thermopräzipitinreaktion als allgemeine serodiagnostische Methode: Ihre Anwendung bei der Diagnose des Schweinerotlaufs, *Berl. tierärztl. Wchnschr.* **28**:165-167, 1912.

26. Schoening, H. W.; Creech, G. T., and Grey, C. G.: A Laboratory Tube Test and Whole-Blood Rapid Agglutination Test for the Diagnosis of Swine Erysipelas, *North Am. Vet.* **13**:19-25, 1932.

27. Jadassohn, W., and Mu, J. W.: Ueber die Immunbiologie der Haut beim Rotlauf (Erysipeloid), *Arch. f. Dermat. u. Syph.* **162**:210-216, 1930.

28. Schoening, H. W., and Creech, G. T.: Serological Studies of Swine Erysipelas with Particular Reference to Agglutination, *J. Agric. Research* **50**:71-79, 1935.

29. Ingram, J. T., and Stuart, R. D.: Erysipeloid, *Brit. J. Dermat.* **46**:303-308, 1934.

30. Bierbaum, K., and Gottron, H.: Zur Kenntnis des Erysipeloids Rosenbach unter besonderer Berücksichtigung seiner Beziehungen zum Schweinerotlauf, *Dermat. Ztschr.* **57**:5-27, 1929.

31. Biberstein, H.: Untersuchungen über Hautreaktionen bei menschlichen und tierischem Rotlauf, *Arch. f. Dermat. u. Syph.* **168**:146-160, 1933.

Jadassohn and Mu²⁷ infected and reinfected rabbits by the intracutaneous route. The lesions produced were more localized, indurated and nodular, and the erythema was smaller in area, when the animal had been previously inoculated. Biberstein³¹ found that 88 per cent of patients with active infections reacted to the intracutaneous injection of fresh erysipelotheix vaccine or even old filtrates of killed cultures (erysipeloidin).

The group of hogs with erysipelotheix infection which Nieberle³² described had previously been vaccinated with a combination of immune serum and virulent erysipelotheix. A characteristic form of cutaneous necrosis and sloughing occurred, which showed, in sections, swelling of the dermal collagen, degeneration of fibroblasts, hyaline thrombosis of dilated capillaries and arterioles and hyalinization of the walls of blood vessels. Nieberle saw a similarity between these alterations, which he interpreted as expressions of hyperergy, and those of the Arthus phenomenon and suggested that there may occur a reaction in the skin between the antigen produced in the current infection and the immune bodies resulting from the prior vaccination.

Further studies are required to clarify the states of altered reactivity which may be induced by an initial erysipelotheix infection. From the available evidence it seems likely that in the case reported in this paper a prior episode of the disease, the clinical form of which was that of erysipeloid of Rosenbach, existed during the three weeks before the patient's admission to the hospital and induced a hyperergic state which influenced the reaction to subsequent reinfection.

Several differential counts revealed an increase of polymorphonuclear leukocytes but not of monocytes. Egehøj³³ has reported monocytosis in swine, and Klauder¹ in man.

According to Gans,³⁴ the histology of the cutaneous lesions is not well known. His description, like those of Delbanco,³⁵ Bazzoli³⁶ and Callomon,¹² stresses the relative absence of changes in the epidermis and the presence of serous inflammation, especially of the corium, with widening of lymph spaces and dense perivascular infiltration of lymphocytes and mast cells. The changes in the epidermis reported by Cheval-

32. Nieberle, K.: Ueber hyperergische Hautentzündung beim Schwein, Verhandl. d. deutsch. path. Gesellsch. **26**:239-243, 1931.

33. Egehøj, J.: Similarity of Blood Picture in Erysipelas of Swine and Infectious Mononucleosis of Man, Ugesk. f. læger **99**:698-699, 1937.

34. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, vol. 1, pp. 335-336.

35. Delbanco, E.: Ueber das Erysipeloid, Deutsche Med.-Ztg. **19**:781-784, 1898.

36. Bazzoli, L.: Il mal rossino e l'eresipeloide, Arch. ital. di dermat., **sif. 2**: 449-472, 1927.

lier and associates,³⁷ namely, edema, leukocytic infiltration and necrosis of the islands of cells in the malpighian layer progressing to the formation of vesicles, parallel closely those observed in the first specimen in the present case.

Relatively few histologic reports on cutaneous lesions in swine have been recorded. In a recent report (Weidman, in Klauder¹) the description underlines the fact that the cleaning and dehairing technics to which slaughtered hogs are subjected in the packing houses result in the loss of the epidermis and often of the upper portion of the cutis and render the material unsuitable for study.

Penicillin administered intramuscularly in a dose of 20,000 units every three hours for several days brought about moderate improvement; doubling the dose resulted in a dramatic clinical recovery. In all, the patient received 8,000,000 units during twenty days.

SUMMARY

An erysipelothrux infection of a human being, who acquired it by direct contact with a hog suffering from swine erysipelas, was distinguished clinically by the extremely rapid dissemination of the eruption, the severe pruritus and the development of huge bullae. These features and the histologic observations, particularly the swelling of the collagen, the numerous eosinophils in the infiltrate, the capillary engorgement and the serohemorrhagic edema of the dermis, indicate that the unusual manifestations of the disease may have had an allergic basis. A previous erysipelothrux infection of localized character probably induced the hyperergic state.

Intensive treatment with penicillin effected a complete recovery.

37. Chevallier, P.; Colin, P.; Levy-Bruhl, M.; Ely, L., and Moricard, R.: Fin de l'observation de rouget du porc generalisé chez l'homme, Bull. Soc. franç. de dermat. et syph. **39**:106-112, 1932.

ACTINOMYCOSIS DUE TO NOCARDIA ASTEROIDES

Report of Two Cases

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SINCE aerobic types of *Actinomyces* may be highly pathogenic to man and are not so well known as the anaerobic *Actinomyces bovis*, the death of 2 patients infected with an aerobic variety appears worthy of record, not only because of the rarity of the organism, but also to emphasize the necessity of accurate diagnosis and vigorous therapy.

In 1891, Eppinger¹ reported the finding of an aerobic gram-positive, acid-fast actinomyces in cerebral abscesses and meningeal exudate of a man who became delirious and died in two weeks. This organism readily grew on ordinary mediums as small starlike colonies, due to the radiating filaments, and was named *Cladothrix asteroides*. It has since been known as *Streptothrix eppingeri*, *Streptothrix asteroides*, *Oospora asteroides* and *Actinomyces asteroides*, and is now called *Nocardia asteroides*.²

In 1921, Henrici and Gardner³ were able to collect but 26 reported cases of infections with aerobic acid-fast *Actinomyces*, and the causative organisms fell into three different types, which differed chiefly in the color of the growth on solid medium and in other minor biologic characters. All but 3 of these 26 cases were apparently of pulmonary origin, and all but 1 were fatal. Henrici and Gardner also reported a fourth type, which they isolated from the sputum of a 31 year old woman with a cough of three years' duration. It differed slightly from the three types

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1. Eppinger, H. L.: Ueber eine neue, pathogene *Cladothrix* und eine durch sie hervorgerufene Pseudotuberculosis, Beitr. z. path. Anat. u. z. allg. Path. **9**:287, 1891.

2. (a) Drake, C. H., and Henrici, A. T.: *Nocardia Asteroides*, Am. Rev. Tuberc. **48**:184, 1943. (b) Waksman, S. A., and Henrici, A. T.: The Nomenclature and Classification of the Actinomycetes, J. Bact. **46**:337, 1943.

3. Henrici, A. T., and Gardner, E. L.: The Acid-Fast Actinomyces, with a Report of a Case from Which a New Species Was Isolated, J. Infect. Dis. **28**:232, 1921.

previously described, and because of the chalky white appearance of the growth, was named *Nocardia gypsoides*. Later, Henrici⁴ reported that after repeated subcultures the strain had become almost identical with *N. asteroides*. Baldacci⁵ proposed reducing *N. gypsoides* and the related strains of aerobic acid-fast *Actinomyces* with only minor differences in their biologic characters to the rank of variants of *N. asteroides*.

In 1937, Goldsworthy⁶ reported a fatal case of pulmonary actinomycosis in a man of 69 years from whose sputum a variant *N. asteroides* had been isolated.

Kessel and Goolden,⁷ in 1938, in comparing eleven strains of *Actinomyces* recovered from human lesions, included 1 case in which cultures taken from the lungs, and the meninges at autopsy yielded an aerobic organism dispersed in branching filaments that did not produce granules and which seemed identical with *N. asteroides* 323 from the American Type Culture Collection.

Benbow, Smith and Grimson⁸ in 1944, reported 2 cases of *N. asteroides* infection with pulmonary and multiple subcutaneous abscesses and sinuses, with a cerebral abscess suspected in 1. The organisms were isolated from the sputum and subcutaneous lesions of both. Treated by bed rest, surgical drainage, vitamins, sulfonamide drugs, iodides and roentgen therapy, both patients made slow but steady improvement and apparently were well after a year.

In 1945, Binford and Lane⁹ isolated *N. asteroides* from a chronic suppurative pneumonitis, massive cerebral abscess and ischiorectal abscess found at necropsy in a man aged 51 under observation for a suspected tumor of the brain.

It is noteworthy that 28 of the 32 persons reported infected with *N. asteroides* were dead at the time the reports were published. In 20 of the cases diagnosis was made only at necropsy, and the organism was demonstrated in 12 during life but usually in the terminal stage of the disease. Twenty-eight cases were of pulmonary infection, and the brain was the site of metastases in at least 10. Of the 4 patients who

4. Henrici, A. T.: *Molds, Yeasts and Actinomycetes*, New York, John Wiley & Sons, Inc., 1930, p. 249.

5. Baldacci, E.: *Revisione di alcune specie del G. Actinomyces*, *Mycopathologia* **1**:68, 1938.

6. Goldsworthy, N. E.: *Pulmonary Actinomycosis Caused by an Acid-Fast Species of Actinomyces*, *J. Path. & Bact.* **45**:17, 1937.

7. Kessel, J. F., and Goolden, E. B.: *Comparison of Strains of Actinomyces Recovered from Human Lesions*, *Am. J. Trop. Med.* **18**:689, 1938.

8. Benbow, E. P., Jr.; Smith, D. T., and Grimson, K. S.: *Sulfonamide Therapy in Actinomycosis: Two Cases Caused by Aerobic Partially Acid-Fast Actinomyces*, *Am. Rev. Tuberc.* **49**:395, 1944.

9. Binford, C. H., and Lane, J. D.: *Actinomycosis Due to Nocardia Asteroides*, *Am. J. Clin. Path.* **15**:17, 1945.

survived, 1 was cured by amputation of the infected foot; another³ was treated with an antigen made from the cultures, but after a year it appeared that the disease had progressed so that the patient had cough, sputum, pulmonary hemorrhages, pain referable to the chest and loss of weight, and the final outcome is not known; the other 2 were apparently cured of infections of the lungs and the chest wall by surgical drainage, sulfonamide compounds, iodides and roentgen therapy. It seems probable that if an early diagnosis were established and adequate therapy instituted the mortality rate might be considerably reduced.

Two cases of infection with aerobic *Actinomyces* will be reported.

REPORTS OF CASES

CASE 1.—A white retired banker of 63 entered Stanford Hospital on Feb. 27, 1943, because of cough and fever for about six weeks. The family and past history were not contributory, except that he had had mild diabetes mellitus for fifteen years, well controlled by small doses of regular insulin. He lived in a small town in central California, had not been in the San Joaquin Valley for years, and had no known contact with parrots, poultry, livestock or persons with pulmonary disease.

The present illness began in January with a hacking cough, dry at first, but later productive of about a cupful of thick, foul, yellow-green, occasionally blood-tinged sputum daily. General malaise, night sweats, fever and anorexia appeared, and he lost 40 pounds (18.1 Kg.) in weight. A diagnosis of bronchitis was made by his local physician, and he was treated with sulfadiazine for a few days without improvement. He was referred to Stanford Hospital.

Physical Examination.—The temperature was 38.5 C. (101.3 F.), the pulse rate 100, the respiration rate 24, the blood pressure 138 systolic and 80 diastolic and the weight 65.9 Kg. (145 pounds). He was thin, appeared acutely ill and coughed frequently, bringing up large amounts of foul, greenish yellow sputum. His skin was warm and moist, and there were no petechiae. Moist rales were heard throughout both lung fields, but there was no dullness to percussion, and no signs of cavitation could be made out. The liver, the spleen and the lymph nodes were not enlarged. No other abnormalities were found on physical examination.

Laboratory Examination.—The red blood cell count was 3,700,000, hemoglobin 10.3 Gm. per hundred cubic centimeters and white blood cells 21,600, with polymorphonuclear cells 86 per cent (banded 35 per cent and segmented 51 per cent), lymphocytes 12 per cent and monocytes 2 per cent. The urine was normal. Smears and cultures of the sputum were thought to contain only the usual nasopharyngeal flora, and the presence of long slender branching gram-positive filaments was not considered significant. No acid-fast bacilli were recovered from the sputum by culture or guinea pig inoculation following concentration with sodium hydroxide. Cultures of the blood and urine gave negative results. Roentgenograms of the chest showed scattered infiltrations in the right upper lobe and in the left upper and lower lobes (fig. 1).

Course.—The course is graphically summarized in figure 2. Sulfadiazine was administered in full doses for a week, during which the temperature fell to normal and the patient felt much better. There was a relapse five days after adminis-

tration of the drug was stopped, with high fever and an increase in cough and sputum. Sulfadiazine was again given in full doses for nine days, and the temperature fell to normal on the sixth day of therapy. A second relapse occurred four days after treatment with the drug was discontinued, with high fever and a further exacerbation of cough and sputum. Roentgenograms showed a definite spread of the patchy infiltration of both lung fields, but on careful study of the sputum again no organism was recognized as the cause. The diabetes was well controlled with morning injections of 32 units of protamine zinc insulin and 16 units of crystalline zinc insulin, except when the temperature was elevated, when it was necessary to increase the protamine zinc insulin dose to 50 or 60 units. After ten days of high fever, sulfadiazine was administered, 6 to 8 Gm. a day for nine days, and the temperature gradually subsided to normal. In spite of this, the white blood cell count rose to 50,000, with 98 per cent polymorphonuclear leukocytes; cough and sputum continued, and the patient seemed to be getting worse. When the fever reappeared five days after the administration of sulfadiazine was stopped, a roentgenogram of the chest showed a further spread

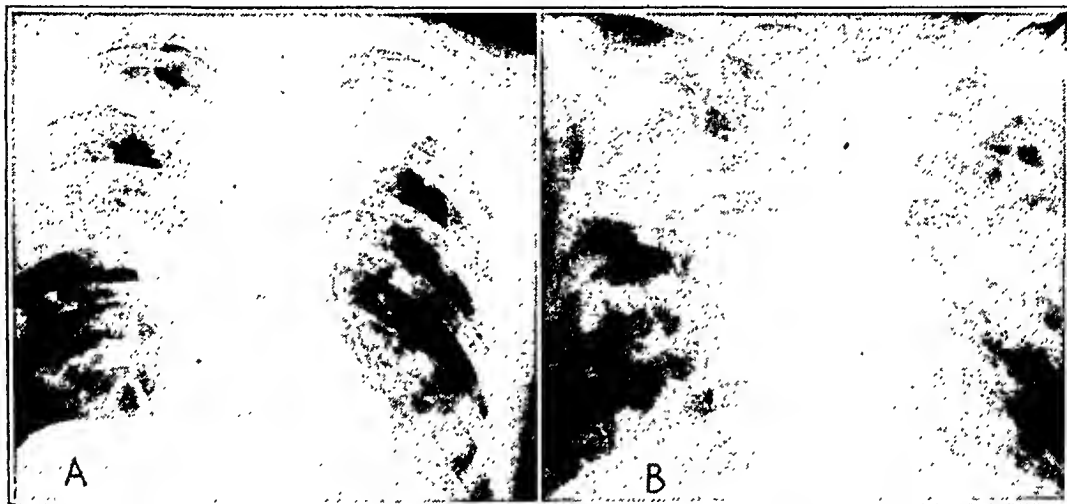


Fig. 1 (case 1).—*A*, appearance of chest on Feb. 26, 1943, showing scattered infiltrations in the upper lobe of the right lung and in the upper and lower lobes of the left. *B*, chest on May 10, 1943, showing extensive involvement of both lung fields.

of the infiltrations in both lung fields, especially in the upper half of the right lung, and a small amount of fluid was present at the base of the left lung. There appeared to be several small cavities in both lungs. Physical examination revealed coarse rales over both lung fields without definite signs of cavitation, and there was dullness at the base of the left lung. The liver and the spleen were not palpable, and there was no adenopathy.

Roentgen therapy, a total of 225 r, was given from April 26 to April 29 in view of the possibility that the infiltration in the lungs might be caused by atypical Hodgkin's disease. This was stopped when branching mycelial filaments, present in smears of the sputum since entry, were cultured and tentatively identified as a *Streptothrix*. At this time, firm, purplish nodules with fluctuant centers began to appear in the subcutaneous tissues all over the body, but were most prominent over the upper extremities, anterior part of the thorax and the abdomen. Some were fixed to the skin; others were deeper, and all were surprisingly free of tenderness. Thick greenish yellow pus was aspirated from

several of these nodules, and both smears and cultures contained the same organism that was isolated from the sputum. It was also isolated in pure culture from blood drawn on May 3.

It was now evident that the patient was suffering from a fungous infection of the lungs, with a diffuse hematogenous spread to the subcutaneous tissues, and presumably to other organs as well. He was weak and apathetic and ate little, requiring a drastic reduction of his insulin dose. The process continued to spread throughout both lung fields, and he was able to bring up only small amounts of sputum. The extensive involvement of both lungs, in contrast to the early infiltrations on entry, is clearly illustrated by reproductions of the roentgenograms of the chest of February 26 and May 10 (fig. 1).

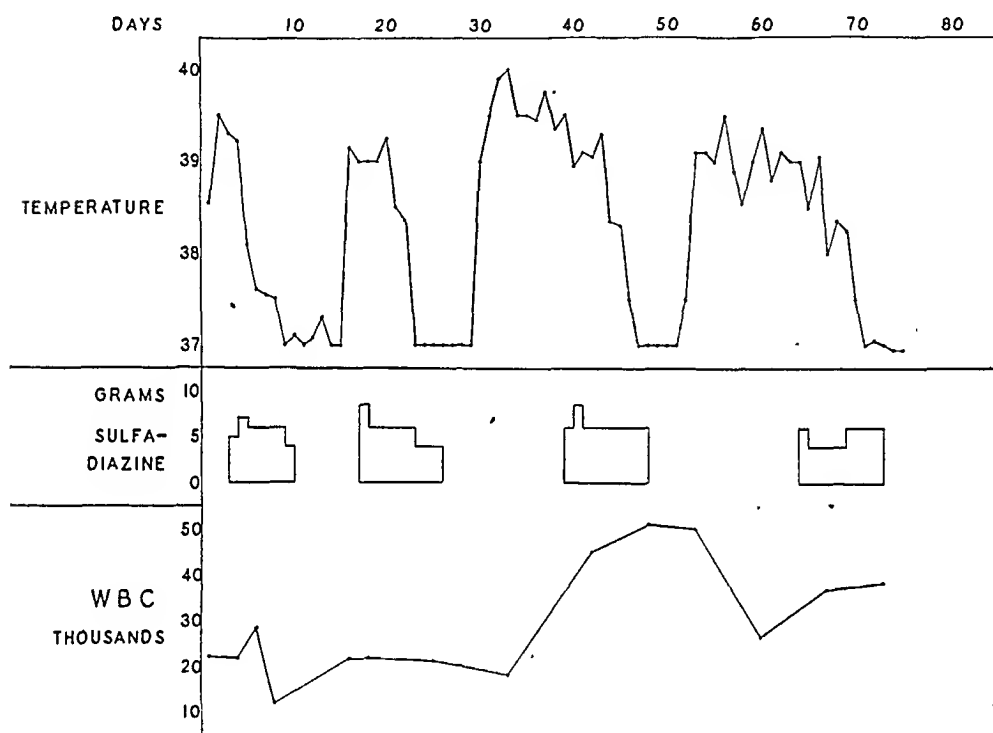


Fig. 2 (case 1).—Chart showing the beneficial effect of sulfadiazine on the temperature curve, and the considerable leukocytosis.

Four to 6 Gm. of sulfadiazine was given daily until he became oliguric, with a great amount of sulfadiazine and numerous red cells in the urine on May 9. The drug was stopped and fluids forced, and urine again flowed freely. The fever subsided, but he failed rapidly, became disoriented and then unconscious, and died on May 11.

Autopsy.—Examination seven hours after death revealed an emaciated elderly man with many firm to fluctuant nodules, 1 to 2 cm. broad, beneath the skin of the trunk, arms and legs which contained thick yellow-green exudate. None had developed sinuses. The pectoral, anterior abdominal and psoas muscles contained similar abscesses. The peritoneal and pleural cavities were free of fluid, but the latter were largely obliterated by dense adhesions.

Heart: The heart weighed 400 Gm. The myocardium of both ventricles contained several abscesses 3 to 10 mm. in diameter, some just beneath the intact epicardium

and others showing through the intact endocardium. The right ventricle was slightly dilated and hypertrophied. The coronary arteries and aorta were moderately atheromatous.

Lungs: The left lung weighed 1,430 Gm., and the right, 1,500 Gm. The ragged pleurae were irregularly thickened. Cut surfaces of both lungs were studded with yellow-gray opaque nodular areas of infiltration and abscesses up to 2 cm. in diameter, with thick yellow-green exudate in the centers (fig. 3).



Fig. 3 (case 1).—Photograph of the cut surface of the right lung, showing multiple abscesses up to 2 cm. in diameter.

Between these areas the lungs were wet and hyperemic. The peribronchial lymph nodes were large and black with occasional small abscesses.

Thyroid: The normal-sized gland contained a 1 cm. abscess in the left lobe. The parathyroids were normal.

Spleen: The spleen weighed 250 Gm. The capsule was smooth, and the cut surface firm and hyperemic, with a single 0.5 cm. subcapsular abscess.

Kidneys: The kidneys weighed 200 Gm. each. The capsules stripped readily, leaving faintly granular surfaces with scattered abscesses from 2 to 15 mm. in diameter. On sectioning, these were found in both cortex and medulla. The pelves contained many fine crystals of sulfadiazine, and the intact mucosa was dull and hyperemic. The ureters were patent, and the bladder contained 500 cc. of turbid yellow urine.

Gastrointestinal Tract: The esophagus, the stomach, the appendix and the small and the large intestine were normal except for several 8 mm. abscesses in the wall of the midileum, which did not penetrate the mucosa or serosa, multiple false diverticula in the descending colon, and firm, almost black, feces in the colon.

The liver, the gallbladder, the adrenals, the pancreas, the prostate, the testes, the seminal vesicles and the vertebral marrow appeared normal.

Head: The scalp, the skull, the meninges and the brain were normal except for moderate atherosclerosis of the vessels of the circle of Willis. Multiple cut surfaces of the formaldehyde-fixed brain revealed no abscesses or abnormalities.

Microscopic Examination.—**Lungs:** The pleura was thickened with vascularized fibrous tissue. There were multiple abscesses in the lungs with necrotic debris, myriads of neutrophils and delicate gram-positive mycelial threads in the lumen. The alveolar septums had completely disappeared in these areas but were visible at the periphery, where the alveoli were filled with fibrin and neutrophils or fibroblasts and organized exudate containing lymphocytes, plasma cells and large mononuclear cells. In other areas, there were bronchopneumonic patches of fibrin, neutrophils and phagocytes with much nuclear debris, but no necrosis of the septums. Small bronchioles were entirely filled with purulent exudate. In several areas, moderately large blood vessels at the borders of abscesses were partially thrombosed and destroyed in the necrotizing process. Many alveoli were filled with edema fluid, and fairly large patches were well aerated.

Heart: The abscesses contained chiefly neutrophils in various stages of necrosis with walls of cellular fibrous tissue rich in lymphocytes, plasma cells and macrophages. The bordering myocardium showed fatty degeneration. The intima of branches of the coronary arteries was atherosclerotic.

Lymph Nodes: The peribronchial nodes were dark with carbon, and the sinuses contained many neutrophils and phagocytes. One node contained an abscess and another contained nodular fibrosis suggestive of healed tuberculosis.

Skin: Several sections contained discrete subcutaneous abscesses which had necrotic centers, myriads of neutrophils, and delicate beaded, branched gram-positive and gram-negative filaments 1 micron or less in diameter. These were best seen in the purulent exudate at the periphery of the abscess. There were no other bacteria. The filaments showed elongated oval thickening and were not acid-fast to acid-alcohol. The outer zone of the abscesses contained lymphocytes and large mononuclear cells.

Kidneys: The abscesses were as described in other tissues, and the adjacent tubules contained necrotic debris and neutrophils. Glomeruli showed no intercapillary sclerosis as seen at times in diabetes mellitus. The pelvis was largely denuded of epithelium, the submucosal vessels were hyperemic, and a small amount of purulent exudate covered the surface.

Pancreas: The islets were normal, but there was a mild increase in inter-acinar and interlobular fibrous tissue with moderate numbers of lymphocytes.

Brain: The brain and meninges were normal.

Abscesses in the spleen, ileum, thyroid and muscles were as described in other organs.

Culture of Heart Blood.—A blood culture taken from the heart at autopsy remained sterile after three months.

Mycology.—The slender branching myceliums found in the sputum (fig. 4 C), pus from the subcutaneous abscesses and the blood stream during life and from

multiple lesions at necropsy were gram-positive, finely and coarsely granular and were entirely decolorized by the acid-alcohol of Ziehl-Neelsen carbolfuchsin stain. They were weakly acid-fast when an aqueous solution of sulfuric acid was used for decolorization.^{2a} The filaments were single or in small loose clusters without

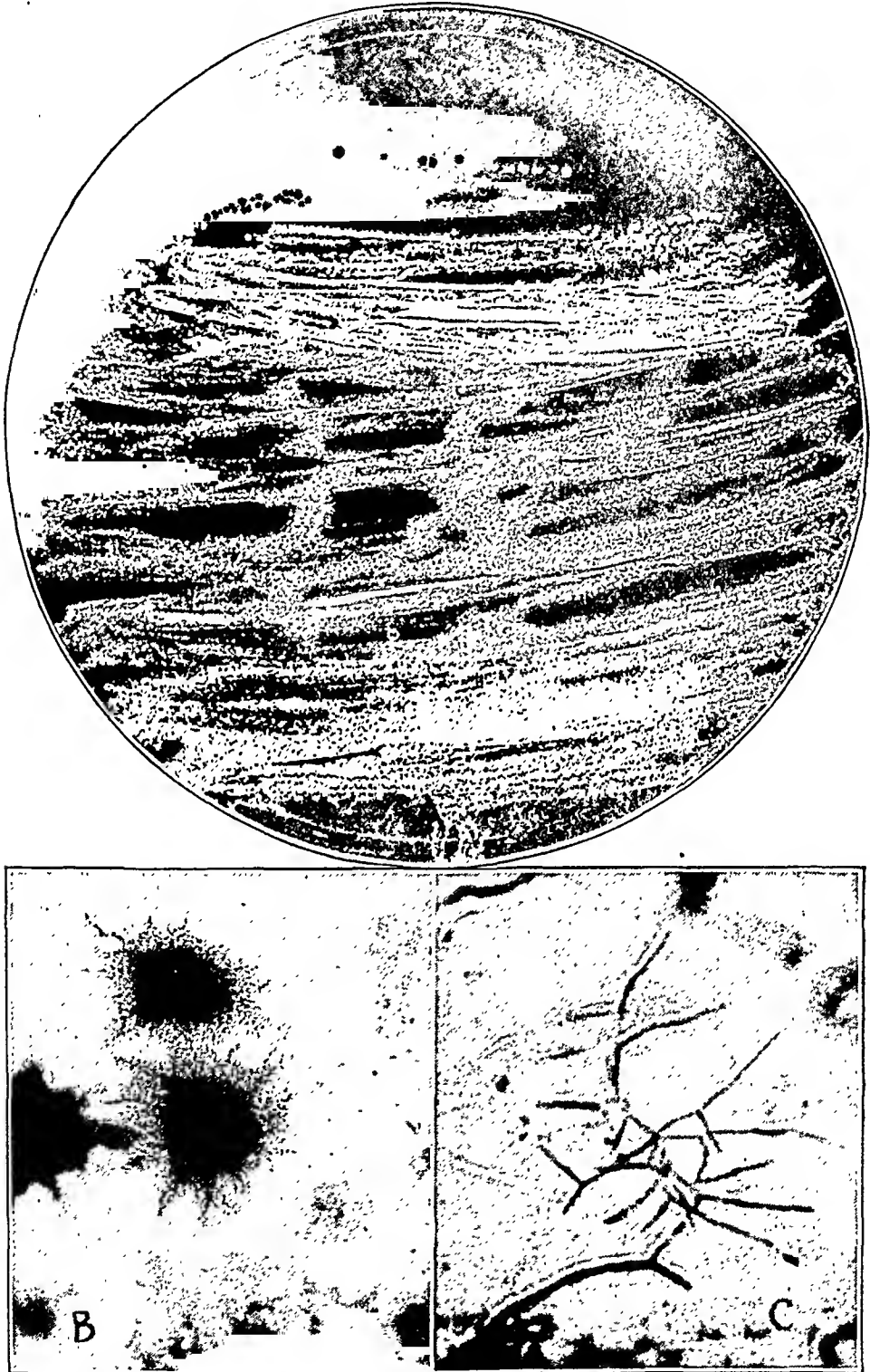


Fig. 4 (case 1).—*A*, photograph of culture of *N. asteroides* on nutrient agar, after two days (actual size). *B*, photomicrograph of culture of *N. asteroides* in a poured plate of nutrient agar showing the starlike colonies, after four days ($\times 110$). *C*, photomicrograph of sputum stained by Gram's method showing branched mycelia ($\times 1,300$).

club formation. Cultures of the subcutaneous abscesses and blood were pure and grew readily on blood agar, nutrient agar and Sabouraud's medium incubated aerobically at 37 C. In twenty-four hours there was a hazy growth on the plates, but in forty-eight hours the small white colonies, some smooth and glistening and others rough and dry, and all quite adherent to the medium, were as prominent as on the plate shown in figure 4A. When stained, they appeared as gram-positive bacillary and coccoid forms and as branched filaments, but when transferred to thioglycolate broth they grew as branching filaments in a pellicle on the surface. Within a week, some of the colonies on solid mediums were yellowish, and then became pale orange. There was a variation in the pigmentation of different colonies. Older cultures showed a white feathery surface. The starlike colonies described by Eppinger¹ are well illustrated in the poured agar plate (fig. 4B). This organism caused no change in litmus milk, and gelatin was not liquefied.

Cultures were submitted to Dr. C. W. Emmons, Principal Mycologist of the United States Public Health Service at the National Institute of Health, Bethesda, Md., and to Dr. N. F. Conant, Duke University School of Medicine, Durham, N. C., both of whom identified the organism as *N. asteroides*. Some of the tissues removed at necropsy were examined by Dr. Roger D. Baker, Duke University, who verified the presence of this organism in the lesions.

Summary.—The patient complained of a cough which was productive of much sputum, and lost weight. Roentgenograms showed infiltrations of both lungs. After three and a half months in the hospital, he died of a generalized infection due to *N. asteroides* with multiple metastatic abscesses apparently spread from the lungs. His sputum, subcutaneous abscesses and blood stream contained the fungus. He responded well to trials of sulfadiazine therapy, but, unfortunately, the etiologic agent was not recognized until too late in the course of the disease. His diabetes was probably favorable to the development and spread of the infection.

CASE 2.—A white housewife of 49 entered Lane Hospital on April 3, 1945, because of headaches, nausea and vomiting for one month. Her father had died of diabetes mellitus at 44 and her son and daughter had had "nervous breakdowns." The patient had always been healthy except for influenza and pneumonia in 1919, following which bilateral deafness developed. Her fallopian tubes had been ligated, and the appendix removed in 1923. She lived in Stockton, in central California.

Present Illness.—She tired easily, required much rest and sleep and complained of frequent headaches for six months. Pounding occipital headaches, radiating to the left, became so severe during the last month that she was nauseated and vomited frequently. These attacks occurred most often during the night. Her vision failed, she became dizzy, and frequently she lost her balance in walking.

Physical Examination.—Her temperature was 37.8 C. (100.04 F.), her pulse rate 100, her respiration rate 20, her blood pressure 160 systolic and 100 diastolic, her height 157 cm. (62 inches) and her weight 81.8 Kg. (180 pounds). She was obese, complained bitterly of headaches and frequently expectorated small amounts of vomitus. The physical and neurologic findings on entry were negative, except for bilateral choked disks (4 D.), central scotomas and enlarged blindspots, engorged fundic vessels with some small hemorrhages around the disks and poor hearing. The gait was not tested because of nausea and headache on raising her head.

Laboratory Examination.—The red blood cell count was 6,600,000, hemoglobin 18.3 Gm. per hundred cubic centimeters and white blood cells 16,600, with polymorphonuclear cells 87 per cent (banded 4 per cent and segmented 83 per cent), lymphocytes 10 per cent and eosinophils 2 per cent. The Wassermann reaction of the blood was negative. The urine was normal. Roentgenograms of the skull showed no evidence of intracranial abnormalities.

Course.—Transient paresis of the right and left external rectus muscles developed, and her vision was subjectively worse. On April 6 she complained of unusually severe headache, her breathing was irregular, her fingers were cyanotic, and she lost consciousness for a few minutes, during which Hoffman's sign was bilaterally positive, Babinski's sign was negative, and reflexes of the upper extremities were hyperactive. A lumbar puncture showed an initial pressure of 270 mm. of water and a resting pressure of 215, with normal dynamics. The fluid was faintly bloody at first, but after less than 2 cc. was withdrawn it was clear and colorless. It contained 762 red blood cells, no white blood cells and 25 mg. of protein per hundred cubic centimeters; the Wassermann reaction was negative, and the colloidal gold test was read as 1223221100. She was often confused mentally and was noisy, and her headaches were poorly controlled by codeine. Ventriculography was contemplated, but on April 8, ten minutes after speaking lucidly to a nurse, she was found dead. Her blood pressure ranged from 220 systolic and 126 diastolic to 112 systolic and 80 diastolic during the five days that she was in the hospital, and her temperature gradually fell to 37 C. (98.6 F.). The clinical impression was an intracranial lesion, possibly a cerebral tumor or a vascular accident, with no localizing signs.

Autopsy.—Examination fifteen hours after death revealed a short, obese, middle-aged woman with an old white lower midline abdominal scar, subcutaneous lipomas on her ankles and no edema. The peritoneal and pleural cavities were free of fluid, but the midlateral area of the upper lobe of the right lung was adherent to the pleura.

Heart: The heart weighed 350 Gm. There was considerable subepicardial fat, and the chambers, valves, myocardium and coronary vessels were normal.

Lungs: Each lung weighed 450 Gm. All lobes were practically normal, except for slight edema and hyperemia and a localized area of slight pleural thickening with the adhesions described above. The peribronchial lymph nodes were normal but black.

Head: The scalp, skull, meninges and venous sinuses were normal. The brain weighed 1,350 Gm. The convolutions were smoothly flattened, and fluid was practically nil. The vessels of the circle of Willis were normal. The cerebellum showed distinct markings where it had been forced into the foramen magnum. An incision into a bulging fluctuant area in the posterior portion of the right lobe of the cerebellum caused thick greenish exudate to well forth. The exudate was semitranslucent and contained no granules. Sectioning of the cerebellum revealed an irregular 2.5 cm. abscess with a soft wall extending to within 1 cm. of the posterior medial border of the right lobe and not communicating with the fourth ventricle. The fluid in the normal-sized ventricles and in the foramen magnum was clear. The middle ears, mastoid cells and frontal, ethmoidal and sphenoidal sinuses appeared normal. Further sectioning of the formaldehyde-fixed brain revealed no other abnormalities.

Other abnormal findings at the autopsy were cholesterosis of the gallbladder, a small mural fibromyoma of the uterus, multiple false diverticula and a small

pedunculated papilloma of the colon, moderate atherosclerosis of the aorta, absence of the appendix, and no other abscesses.

Culture of Heart Blood.—A blood culture taken from the heart at autopsy remained sterile.

Microscopic Examination.—Brain: The lumen of the cerebellar abscess was filled with necrotic exudate rich in neutrophils and filaments of gram-positive, branched, granular mycelia without clubs. Vascular granulation tissue, containing neutrophils, lymphocytes, vacuolated phagocytes and a few eosinophils formed the wall, with multiple small satellite abscesses. Beyond these, in some areas, there was an increase in fibrous tissue with lymphocytes and plasma cells, while in other areas fibrosis was absent and the inflammatory reaction diffusely blended into the adjacent brain substance. It extended into an outermost folium in one area, and here the meninges contained moderate numbers of lymphocytes and plasma cells and a few neutrophils. The meninges elsewhere in the cerebellum, medulla and cerebral cortex and the choroid plexus were normal; likewise sections from the parenchyma.

Lungs: Many alveoli contained thin edema fluid and debris, suggesting aspiration of gastric contents. The septal capillaries were hyperemic. A section from the area of adhesions over the midportion of the upper lobe of the right lung showed a flat subpleural zone of fibrous tissue surrounding many lymphocytes and hemosiderin-laden phagocytes with no tubercles or areas of suppuration.

Spleen: The splenic sinuses were hyperemic, with pools of blood, suggesting the asphyxial picture. The follicles were small. Moderate numbers of lymphocytes and plasma cells and a few eosinophils and neutrophils were in the pulp.

Bone Marrow: The vertebral marrow was normally active with a preponderance of cells of the myeloid series and many adult neutrophils.

Middle Ears: There was no evidence of inflammation.

Sections of other tissues and organs verified the gross findings and yielded no further pertinent information.

Mycology: Smears, cultures and microscopic sections from the cerebellar abscess showed dispersed branched filaments of a fungus which was identical with the *N. asteroides* described in case 1. It grew readily as a pure culture on ordinary mediums when incubated aerobically at 37 C. Like the organism of case 1, it was not acid-fast to acid-alcohol, but was weakly and irregularly acid-fast to aqueous, sulfuric acid.

Summary.—The patient had severe headaches, nausea and vomiting for a month. She entered the hospital for study but died in five days with the clinical diagnosis of an intracranial lesion without localizing signs. Her temperature was practically normal, and there was a moderate neutrophilic leukocytosis. Autopsy revealed a large cerebellar abscess containing *N. asteroides*. The lungs must be considered as a possible primary focus even though only a small area of fibrosis with lymphocytes and pleural adhesions was found. The middle ears and mastoid cells were normal.

COMMENT

The fungi causing actinomycosis in man belong to two biologic types. The anaerobic type, *A. bovis*, is gram-positive and non-acid-fast and is found in approximately 90 per cent of the cases of clinical actinomycosis.⁸ It usually produces "sulfur granules" in the tissues, made up of mycelial masses with radial club arrangement of the periphery. This club for-

mation is such a classic part of the description of this organism that in its absence the detection of *Actinomyces* may be confusing. The aerobic type includes several species, all of which are gram-positive and some of which are partially acid-fast. The latter may form granules without clubs or may be dispersed in branching filaments.⁷ The aerobic *N. asteroides* is of this type and has been studied the most extensively. It is highly pathogenic for man. Benbow, Smith and Grimson⁸ propose that since the signs, symptoms, course of the disease and response to treatment are so nearly identical in the two types of infection that the disease should be called actinomycosis.

Our case 1 illustrates the ease with which the presence of a pathogenic fungus may be disregarded in examinations of sputum and cause an unfortunate delay in arriving at the correct diagnosis. Although mycelia were seen in the smears, the organism was not successfully cultured on early attempts and was regarded merely as a harmless contaminant. It is not surprising that cultures and guinea pig inoculations gave negative results when the sputum was concentrated by the sodium hydroxide method, because *N. asteroides* is killed by this procedure.⁹

The gross and histologic appearance of the specific lesions in both of our cases were those of an acute pyogenic inflammation with a central zone of liquefactive necrosis and numerous polymorphonuclear leukocytes. There was no distinct caseation, no epithelioid tubercles and no giant cells. About the area of liquefaction was a zone of granulation tissue with neutrophils, lymphocytes and plasma cells and at times varying amounts of slightly more dense fibrous tissue. The dispersed mycelia of the fungus were not seen in the hematoxylin and eosin stains but were readily visible in the sections stained by Gram's method. The subcutaneous abscesses did not form fistulas or sinuses.

THERAPY

Since 1938, there have been many reports indicating the effectiveness of the sulfonamide compounds in the treatment of actinomycosis caused by *A. bovis*. These are summarized in the papers by Dobson, Holman and Cutting in 1941,¹⁰ and by Dobson and Cutting in 1945.¹¹ The success of Benbow, Smith and Grimson⁸ in curing 2 cases of actinomycosis caused by *N. asteroides* indicates that the sulfonamide compounds are equally effective in both the aerobic and the anaerobic type of this fungus. This is supported by a study of figure 2, which shows a striking correlation between the temperature curve and the

10. Dobson, L.; Holman, E., and Cutting, W.: Sulfanilamide in the Therapy of Actinomycosis, *J. A. M. A.* **116**:272 (Jan. 25) 1941.

11. Dobson, L., and Cutting, W.: Penicillin and Sulfonamides in the Therapy of Actinomycosis, *J. A. M. A.* **128**:856 (July 21) 1945.

administration of sulfadiazine in case 1. On four occasions, the high fever disappeared after sulfadiazine therapy, indicating that the drug was highly effective against *N. asteroides*. This was not appreciated until after the third course of sulfadiazine when the entire temperature and therapy records were charted on a single sheet on paper. Had the attending staff been fully aware of the beneficial action of the sulfadiazine, the therapy would have been altered, for it has become axiomatic that the best results in actinomycosis follow prolonged intensive sulfonamide medication. When the diagnosis was finally established the disease was so widespread that intensive therapy was of no avail.

A few reports suggest that penicillin is effective in actinomycosis, but none of the patients have been followed sufficiently long to be certain that relapses will not occur. Dobson and Cutting¹¹ used sulfonamide or penicillin therapy in 16 cases and considered the disease cured in 7 cases and arrested in 7. In 3 cases the disease was reported cured or arrested by penicillin alone, in 3 arrested by penicillin and sulfadiazine and in 6 cured by sulfonamide drugs. In 2 cases in which the latter medication was given, the disease ended fatally. In 1 of the 3 cases in which penicillin alone was given, an apparent cure of cervicofacial actinomycosis was effected by the administration of 4,655,000 units over a thirty-eight day period. Rapid healing in another case of cervicofacial actinomycosis followed the use of 1,560,000 units of penicillin in seventeen days. The third was a case of pulmonary and retroperitoneal actinomycosis in which 4,300,000 units of penicillin in thirty-seven days produced a prompt and decided improvement, so that the disease was considered arrested. They concluded that both penicillin and the sulfonamide compounds are highly effective drugs in the treatment of actinomycosis. There are as yet no reports on the use of penicillin in actinomycosis due to *N. asteroides*.

In vitro tests, made by streaking a broth culture of the *N. asteroides* isolated from our case 1 onto blood agar plates containing varying concentrations of penicillin, revealed that the organism grew as readily in the presence of .05, 0.1, 0.4, 1, 2 and 4 units per cubic centimeter as on the controls. Experience with other infectious diseases indicates that organisms which are resistant to as high concentrations of penicillin as 1 unit per cubic centimeter do not respond well to penicillin therapy in the usual doses. If 0.5 units per cubic centimeter is considered a high therapeutic level for penicillin it would appear from the tests in vitro that eight times this concentration would have no inhibitory effect on the growth of the organism. However, this relationship may be altered by the natural protective mechanisms of the body so that a lesser level may become effective. The results obtained by Dobson and Cutting¹¹ in patients infected with the anaerobic type of this fungus indicate that

penicillin in large doses should be given a thorough trial in patients infected with the aerobic type.

SUMMARY

Infections in man due to the aerobic, partially acid-fast *Nocardia asteroides* are rare as compared to those due to the anaerobic *Actinomyces bovis*. The symptoms, course of the disease and response to therapy are so nearly alike that the disease produced by the two types of fungi should be called actinomycosis. Thirty-two cases of infection with *N. asteroides* have been collected from the literature. The mortality rate appears to be high: 28 of 32 patients were dead at the time the reports were published. The infection was pulmonary in 28 cases, and the brain was the site of metastasis in at least 10. In 2 cases infection of the lungs and the chest wall was apparently cured by surgical drainage, sulfonamide therapy iodides and roentgen therapy.

Two new cases of infection with *N. asteroides* are added in this report. The first of these was of a man of 63, who was hospitalized for three and a half months for cough, sputum, loss of weight and pulmonary disease. He responded well to trials of sulfadiazine therapy, but the etiologic agent was not recognized until late, when the fungus was isolated from his sputum, subcutaneous abscesses and blood stream. At autopsy the lungs, peribronchial lymph nodes, heart, thyroid, kidneys, spleen, intestines, muscles and subcutaneous tissues contained abscesses produced by *N. asteroides*. The second case was that of a woman of 49, who was hospitalized for five days prior to death with a clinical diagnosis of an intracranial lesion without localizing signs. Autopsy revealed an abscess in the cerebellum caused by *N. asteroides*. The lungs are suspected as the primary focus, and no other metastases were found.

It is recommended that patients with actinomycosis due to the aerobic *N. asteroides* be treated with the sulfonamide compounds, and penicillin, as vigorously as are those infected with the anaerobic *A. bovis*, and that surgical drainage, iodides and roentgen ray therapy be used as the indications arise.

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Progress in Internal Medicine.

SYPHILIS

A Review of the Recent Literature

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AND

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BALTIMORE

IN THIS annual review¹ of the recent developments in the field of syphilology, emphasis is placed on subjects of greatest current importance. The publications that appeared from July 1945 to June 1946 are concerned for the most part with research carried on during the years of the war. The prodigious cooperative study of penicillin therapy under the supervision of the wartime Committee on Medical Research; the development under war-borne emergency of dimercaprol ("BAL"; 2,3-dimercaptopropanol), efficacious in the treatment of arsenical poisoning; increased understanding of biologic false positive reactions to serologic tests for syphilis, and advancements in civilian and military control of syphilis—all these bear the imprint of the war stimulus to scientific advancement. The number of journals available for review from war-devastated Europe is negligible.

NEW BOOKS ON SYPHILIS

Merritt, Adonis and Solomon² are the authors of a recently published monograph on neurosyphilis, based largely on their extensive

From the United States Public Health Service and the Johns Hopkins University Venereal Disease Research and Postgraduate Training Center.

1. (a) Moore, J. E.: Syphilis: A Review of the Recent Literature, *Arch. Int. Med.* **56**:1015 (Nov.) 1935. (b) Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **58**:901 (Nov.) 1936; (c) **60**:887 (Nov.) 1937. (d) Padget, P.; Sullivan, M., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **62**:1029 (Dec.) 1938. (e) Moore, J. E., and Mohr, C. F.: Syphilis: A Review of the Recent Literature, *ibid.* **64**:1053 (Nov.) 1939. (f) Mohr, C. F.; Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **66**:1112 (Nov.) 1940. (g) Mohr, C. F.; Padget, P.; Hahn, R. D., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **69**:470 (March) 1942. (h) Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **70**:836 (Nov.) 1942; (i) **72**:635 (Nov.) 1943. (j) Mohr, C. F.; Scott, V.; Hahn, R. D.; Clark, E. G., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **74**:390 (Nov.) 1944. (k) Mohr, C. F.; Scott, V.; Hahn, R. D., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **77**:332 (March); 428 (April) 1946.

and collective experiences at the Boston City Hospital and the Boston Psychopathic Hospital. The approach to the subject is that of the neuropsychiatrist well versed in neuropathology. The various clinical syndromes of neurosyphilis are correlated with the underlying histopathologic changes in the central nervous system in a manner superior to any heretofore available. The discussion of therapy is, however, inferior to the chapters on the clinical and neuropathologic phases.

EXPERIMENTAL SYPHILIS

The albino house mouse (*Mus musculus*) has long been known to be a susceptible carrier of experimental syphilis to rabbits. German investigators have reported that several such European rodents may be used to perpetuate strains of *Treponema pallidum*. These observations led Wile and Johnson² to determine whether mice in this country could be as readily infected. Five different species of native American mice were inoculated intraperitoneally with the Nichols strain of *T. pallidum* (a saline suspension of rabbit testicular syphiloma). All five were found to be capable of harboring the organisms, as determined by inoculations of rabbits, although in the mice the infection uniformly was symptomless.

Wile and Johnson³ also have studied experimentally the course of syphilis in golden hamsters. Syphilis in this animal inoculated with the Nichols strain of *T. pallidum* ran a course similar to that in white mice, i.e., the infection remained clinically inapparent, dark field examination of organs gave negative results, silver impregnation stains revealed no spirochetes, hematoxylin stains showed no histologic changes characteristic of syphilis and the Kahn serologic reaction did not become positive. When, however, tissues (brain, testis or pooled liver, spleen, gonads and heart) from hamsters infected by the intraperitoneal route were inoculated intratesticularly into rabbits, typical syphilomas developed.

SERODIAGNOSIS OF SYPHILIS

Quantitative Serologic Tests.

The importance of quantitative serologic tests for syphilis again is stressed by Callaway,⁵ who has found titrated tests most helpful in

2. Merritt, H. H.; Adams, R. D., and Solomon, H. C.: *Neurosyphilis*, New York, Oxford University Press, 1946.

3. Wile, U. J., and Johnson, S. A. M.: *Experimental Syphilis in Different Species of Native American Mice*, *Am. J. Syph., Gonorr. & Ven. Dis.* **29**:416 (July) 1945.

4. Wile, U. J., and Johnson, S. A. M.: *Experimental Syphilis in the Golden Hamster*, *Am. J. Syph., Gonorr. & Ven. Dis.* **29**:418 (July) 1945.

5. Callaway, J. L.: *Importance of Quantitative Serologic Tests for Syphilis*, *South. Med. & Surg.* **107**:273 (Aug.) 1945.

(1) study of questionable biologic false positive reactions, (2) serologic follow-up of children born of syphilitic mothers, (3) exclusion of the possibility of "zone" phenomena, (4) measurement of the effects of therapy and (5) prediction of the imminence of clinical relapse, which so often is preceded by serologic relapse.

Newer Serologic Procedures.

The "Optimal Zone Reaction."—Kahn⁶ has made a preliminary report of a serologic procedure which he calls the "optimal zone procedure," designed to supplement current serodiagnostic tests. This test is based on an extension of the serum: antigen ratios from 3, used in the standard Kahn test, to 10 or even 15 ratios. By the use of these additional ratios, positive results were obtained in cases of known syphilis which gave seronegative reactions by the usual tests. Also, the author states the belief that negative results with the new procedure following antisyphilitic therapy may be more reliable as an indication of "cure" than negative results with current serodiagnostic tests.

Cardiolipin Antigen.—Improvements in the preparation of cardiolipin antigen⁷ continue to be reported. Pangborn herself⁸ has further simplified the procedure for isolating the substance. The method depends on the fact that cardiolipin is acidic and readily forms stable salts, which may be converted one to another and impurities removed by utilization of the differing solubilities of the several salts in various combinations of solvents. Solutions of cardiolipin may be standardized on the basis of their phosphorus content.

Standard antigens with iodized poppyseed oil for serodiagnostic tests for syphilis, even those prepared under the most carefully controlled conditions, have been subject to variation in sensitivity and specificity. The isolation of cardiolipin from beef heart and the development of methods for the purification of lecithin give promise of antigens whose components can regularly be reproduced. Rein and Bossak⁹ report that cardiolipin antigen, composed of cardiolipin (0.2 per cent) and lecithin (1.3 per cent), may be successfully adopted for use in a micro-flocculation slide test for the serodiagnosis of syphilis. The sensitivity of this antigen was higher than that obtained with Kline diagnostic, Mazzini, Kahn and Kolmer tests as performed at the Army Medical

6. Kahn, R. L.: Optimal Zone Reaction in the Diagnosis and Treatment of Syphilis, *Arch. Dermat. & Syph.* **53**:633 (June) 1946.

7. Pangborn, M. C.: Isolation and Purification of a Serologically Active Phospholipid from Beef Heart, *J. Biol. Chem.* **143**:247 (March) 1942.

8. Pangborn, M. C.: A Simplified Preparation of Cardiolipin, with a Note on Purification of Lecithin for Serologic Use, *J. Biol. Chem.* **161**:71 (Nov.) 1945.

9. Rein, C. R., and Bossak, H. N.: Cardiolipin Antigens in the Serodiagnosis of Syphilis: A Microflocculation Slide Test, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:40 (Jan.) 1946.

Center. This increased sensitivity was obtained without apparent increase in nonspecificity. The specificity of cardiolipin antigen in the presence of malarial infection is described as being "extraordinary," but with serums from patients with leprosy or infectious mononucleosis increased specificity was not apparent.

Kline¹⁰ states the belief that, if further experience confirms the excellent results thus far obtained with cardiolipin antigen, it may be possible to develop a single standard flocculation test for syphilis. In his experience, involving over 2,500 serum tests (including 270 in cases of malaria, over 1,600 on patients with other conditions and over 650 in cases of syphilis), flocculation tests with cardiolipin antigen gave more specific results in nonsyphilitic patients than did Eagle, Hinton, Kahn, Kline and Mazzini antigens and more sensitive results in cases of syphilis than Kline antigen.

Spectrophotometry in Serodiagnosis.—Spectrophotographic methods, now of considerable importance in many branches of chemistry, recently have been applied to serodiagnostic procedures. Of the numerous methods proposed for the standardization of complement, Mayer, Eaton and Heidelberger¹¹ prefer the spectrophotometric procedure for determining complement in terms of "the 50 per cent hemolytic unit." This procedure, they believe, eliminates uncertainties due to subjective factors and furnishes precise and reproducible determinations of complement activity.

Spiegel-Adolf¹² has utilized spectrophotometry in studies of the cerebrospinal fluid. Since most spinal fluids are colorless, spectrographic methods with ultraviolet light must be employed. Three groups of known body constituents absorb ultraviolet light: proteins, lipids and nucleic acids. These substances, therefore, can be detected in the cerebrospinal fluid by ultraspectrophotographic methods. Preliminary studies suggest the presence in the cerebrospinal fluid of patients with dementia paralytica of proteins not normally present in this fluid.

Spinal Fluid Proteins.—Lange¹³ has studied the colloidal gold reaction by analyzing the physicochemical factors involved and by testing various combinations of protein fractions. When various protein fractions were mixed with gold sol in the presence or absence of electrolytes

10. Kline, B. S.: Cardiolipin Antigen in the Microscopic Slide Precipitation Test for Syphilis, *Am. J. Clin. Path.* **16**:68 (Feb.) 1946.

11. Mayer, M. M.; Eaton, B. B., and Heidelberger, M.: Spectrophotometric Standardization of Complement for Fixation Tests, *J. Immunol.* **53**:31 (May) 1946.

12. Spiegel-Adolf, M.: Ultraspectrographic Studies on Cerebrospinal Fluid, *Confinia neurol.* **7**:77, 1946.

13. Lange, C.: Theory of the Colloidal Gold Reaction: I. Reactions Between Gold Sol and Isolated Protein Fractions, *J. Lab. & Clin. Med.* **30**:1006 (Dec.) 1945.

and at p_H 7.4, three qualitatively different reactions were observed: protection, sensitization and coagulation. 1. Protection is produced both by albumins and normal serum globulins in the prezone and by hemoglobin at a p_H above its isoelectric point. 2. Sensitization is produced by serum globulin within an optimal range, electrolytes being required to complete the coagulation. 3. True coagulation, without the assistance of electrolytes, is produced in cerebrospinal fluid only by the pseudoglobulin-like *degenerative protein*¹⁴ indicative of parenchymatous degeneration which elicits the so-called paretic, or plateau, curve.

The author states the belief that the plateau curve is fundamentally different from prezone curves. The latter, in the absence of a *true coagulator*,¹⁴ result from qualitative and quantitative differences of the globulins, while the albumins, as protectors, have only a quantitatively decreasing effect. He also controverts the widely adopted hypothesis that differences in the colloidal gold reaction are produced by alterations in the albumin-globulin ratio. His interpretation is that the changes are regulated by qualitative and quantitative differences in the globulins. The removal of albumins from cerebrospinal fluids, so that any effect of the albumin-globulin ratio is eliminated, produced no qualitative change either in the paretic curve or in the prezone curves.

It has been suggested that a determination of the albumin-globulin ratio in the cerebrospinal fluid might replace the colloidal tests. Several methods have been devised for determining this ratio, all based on the assumption that the globulin present in cerebrospinal fluid is precipitated by 50 per cent saturation with ammonium sulfate. Lange¹⁵ also presents data to indicate that this assumption is true only when considerably higher concentrations of protein than those in normal spinal fluid are present. With relatively low concentrations of protein, which prevail in neurosyphilis, misleading results are obtained by use of 50 per cent saturation with ammonium sulfate to precipitate the globulin. Electrophoretic methods are accurate, but they require such large quantities of spinal fluid as to make them unfeasible in routine practice. With methyl alcohol precipitation, however, Lange expresses the opinion that it is possible to determine consistently accurate albumin-globulin ratios in cerebrospinal fluids both in normal persons and in those with various neurologic diseases. The author emphasizes that the spinal fluid albumin-globulin ratio should be interpreted as an integral part of a complete examination of spinal fluid. He states the belief that the ratio provides information regarding the permeability of the meninges.

14. Italics are Lange's.

15. Lange, C.: Interpretation of Findings in the Cerebrospinal Fluid: II. The Technique and Systematic Interpretation of the Albumin-Globulin Ratio in Cerebrospinal Fluids, J. Lab. & Clin. Med. **31**:552 (May) 1946.

Biologic False Positive Reactions to Serologic Tests.

A review of the entire subject of biologic false positive reactions for syphilis recently has been made by Beerman.¹⁶ This extensive discussion does not lend itself readily to condensation, and the reader is referred to the original article.

The use of mass blood testing as a means of finding syphilis is a time-tested and acceptable procedure in control of syphilis. However, in any mass survey the frequent occurrence of false positive reactions poses a problem of considerable magnitude.

Stokes and his co-workers¹⁷ have summarized the results of an investigation and follow-up on applicants as American Red Cross blood donors found to have positive serologic reactions for syphilis. Of these, only 40.5 per cent were finally adjudged to have syphilis; the remainder (59.5 per cent) were believed to have biologic false positive reactions. In the process of evaluation described, the decision that syphilis actually was present was reached within three months in 69.2 per cent; among those adjudged to have false reactions, the decision was reached within that time in only 22 per cent.

In the differentiation of syphilitic from nonsyphilitic reactions, the authors stress the value of an interpretation of the results of a battery of simultaneously performed sensitive flocculation and complement fixation tests. It was found that the syphilitic positive reaction tended to be of high titer and consistently positive on multiple repetition, with results of precipitation and complement fixation tests confirming each other. The nonsyphilitic reaction was usually of low reagin titer, weakly positive or doubtful but fluctuant, sometimes strongly positive, inconsistent as between flocculation and complement fixation tests, usually more strongly positive in the former than the latter, and tending toward negativity within three months.

In their experience, repeated and carefully interpreted serologic tests were of more value than clinical history, physical examination, heterophile tests, roentgenograms of the chest and study of the patient's family. When clinical evidence of syphilis was present, congenital syphilis and neurosyphilis were the two chief clinical types uncovered by mass serologic testing. The study indicates that with the sensitive modern serodiagnostic tests routine mass blood testing will unearth a disconcertingly high proportion of biologic false positive serologic reactions.

In an effort to determine whether a differentiation between positive serologic reactions due to syphilis and those due to other factors is

16. Beerman, H.: *Biologic False Positive Reactions to the Tests for Syphilis*, Am. J. M. Sc. **209**:525 (April) 1945; **210**:524 (Oct.) 1945.

17. Stokes, J. H.; Boerner, F.; Hitchens, A. P., and Nemser, S.: *Nonspecific Reactions in Routine Blood Testing for Syphilis*, J. A. M. A. **130**:57 (Jan. 12) 1946.

possible with serologic methods now available, Scott and his fellow workers¹⁸ have investigated, in over 1,000 specimens of serum: (a) the "serologic pattern" of acquired and congenital syphilis and of biologic false positive reactions; (b) the serologic reactions of syphilitic and falsely positive serums against nonspecific antigens, and (c) the possible differentiation of truly positive (syphilitic) from biologic false positive reactions by three special serologic procedures (the Kahn "verification" test, a special technic originated by one of the authors [Rein], and the spirochetal complement fixation test).

Under the conditions of the study, which are described in detail, it appeared that:

. . . there is no "serologic pattern" with the tests employed which serves to differentiate "true" from "false" reactions or one type of syphilitic infection (congenital) from another (acquired); that "false positive" sera do not react with nonspecific antigens to a greater extent than do syphilitic sera; and that special, supposedly verifying techniques (Kahn, Rein, spirochetal complement-fixation tests) do not serve to differentiate "true" from "false" positive reactors. As to the latter, on the contrary, it was demonstrated that for all three of these special techniques as employed in this experiment, the type of reaction obtained was a function of the reagin content of the particular serum tested. Low-titered sera, whether from syphilitic or false positive reactors, tended to give the biologic type of reaction with the Kahn "verification" test and Rein special technique, and negative or doubtful results with the spirochetal complement-fixation test; high titered syphilitic sera tended to give the syphilitic type of reaction with the Kahn and Rein tests and positive spirochetal complement-fixation tests; and this correlation between titer and type of reactivity held for at least one animal species (cows). . . .

The results of this, as of previous studies, indicate that biologic false positive sera are usually (though not always) of low titer. Unfortunately, this is not a valid differential point, since the same is true of many patients with syphilis previously treated or untreated, especially the former.

With presently available serologic techniques, therefore, the diagnosis of "true" versus "false" positivity could not be established by examination of a single specimen of serum, either by any single test, "verification" or otherwise, or by any combination of tests. New serologic methods should be developed. Until this is done differential diagnosis between syphilis and other "reagin producing" diseases must continue to be attempted by painstaking clinical examination of the patient, by the weighing of epidemiologic factors (opportunity for infection, examination of sexual and familial contacts), and by serial quantitative serologic tests, repeated over a period of days, weeks, months, or in some cases years.

False Positive Reactions Following Blood Donation.—During World War II there were received from various American Red Cross blood donor centers reports to the effect that occasionally blood donation appeared to result in the transitory appearance of syphilitic reagin in

18. Scott, V.; Rein, C. R.; Schamberg, I. L.; Moore, J. E., and Eagle, H.: The Serologic Differentiation of Syphilitic and False Positive Sera, *Am. J. Syph., Gonorr. & Ven. Dis.* **29**:505 (Sept.) 1945.

the blood of donors. During the war the number of blood donors in the United States ran into the millions. With the increasingly widespread use of routine serologic tests and the zeal with which many physicians institute antisyphilitic therapy on the sole basis of one or more positive reactions, it was important to determine whether blood donation per se may be responsible for the appearance of serologically detectable amounts of reagin in the serum of donors. Unfortunately, despite extensive consideration by the Subcommittee on Venereal Diseases of the National Research Council and several studies under governmental auspices, the situation remains unclarified.

From the statistical analysis of Boynton,¹⁹ it is readily apparent that the incidence of false positive reactions among blood donors cannot be correlated with the actual number of venesections per donor. No clinical data were available on the donors included in this study, although it assumed that those with even temporarily suspicious reactions largely

Data on Positive Serologic Reactions in Presumably Nonsyphilitic Blood Donors (Barnard, Rein and Doan²⁰)

Following	Positive Serologic Reversal (Sic)	Number	Donors in Category	Per Cent
	First donation.....	12	11,299	0.106
	Second donation.....	11	7,694	0.144
	Third donation.....	6	5,709	0.105
	Fourth donation.....	2	3,445	0.058
	Fifth donation.....	0	1,885	0.000

0.413

were self excluded after the first donation following which the question of syphilis arose.

Barnard, Rein and Doan²⁰ have studied the possible role of blood donation as a factor in producing positive serologic reactions in presumably nonsyphilitic donors. Their data are based on groups of American Red Cross blood donors whose positive serologic reactions subsequently were found spontaneously to revert to negative.

A summary of their data, reproduced in the table, indicates that there was a slightly higher percentage incidence of false positive reactions among second time donors than among first time donors and that after the third donation false positive reactions continued to appear, but with diminishing frequency. The authors admit that an incidence of 0.4 per cent is flimsy evidence on which to base a conclusion that

19. Boynton, M. H.: The Incidence of Positive Serologic Reactions in Multiple Blood Donors, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:252 (May) 1946.

20. Barnard, R. D.; Rein, C. R., and Doan, C. A.: False Positive Serologic Tests for Syphilis Following Blood Donation, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:255 (May) 1946.

phlebotomy may cause biologic false positive reactions for syphilis. They accept, however, the questionable statistical validity of their findings, pointing out that the incidence of positive reactions probably would have been higher but for factors of self selection and "weeding out" of actual and potential reactors. Of greater significance, however, is the fact that presumably nonsyphilitic persons have been observed in whom the usually accepted postulates for demonstration of a causal relationship between a nonsyphilitic medical episode (blood donation) and positive serologic reactivity have been fulfilled, i. e. (a) initial seronegativity, (b) confirmed seropositivity without other known cause and (c) spontaneous reversal to negativity.

Boerner, Nemser and Stokes²¹ were unable to demonstrate any significant effect of phlebotomy or of repeated blood donation on quantitative serologic reactions for syphilis. One hundred and twenty-eight prison inmates were the donors. When quantitative complement fixation and quantitative flocculation tests were done immediately before and immediately after withdrawal of 500 cc. of blood, no significant difference in reagin content of the serum was observed. Ninety-seven of these donors were also tested at intervals from the fifth to the fifteenth day following phlebotomy. In none was there any significant change in the serologic reactions. Summarizing their results, the authors state:

Within the limits imposed by the conditions of the experiment, including the limited number of donors used, and by possible confusing elements such as intercurrent infections or other known causes of biologic false positives, and the fallibility of the clinical examination for syphilis as performed, it can certainly not be said that this series reveals the existence of a non-specific positive due to multiple blood donation, or to bleeding as such. Neither can it be said that such a possibility is totally excluded.

Thus, the published reports are at variance, and, on the basis of presently available information concerning the question of whether biologic false positive reactions occur as a result of blood donation alone, the only verdict now possible is one of "insufficient proof."

False Positive Reactions in Malaria.—Biologic false positive reactions to complement fixation tests for syphilis are frequent in the course of malaria. They occur most frequently, according to Babin and Dulaney,²² in a period of six to ten days following an attack of malaria. Interestingly enough, not only does malaria cause false positive serologic reactions for syphilis, but also syphilis causes false positive reactions in the recently developed complement fixation tests for malaria that utilize as antigen

21. Boerner, F.; Nemser, S., and Stokes, J. H.: A Study of the Effect of Bleeding and of Repeated Blood Donation on Serologic Tests for Syphilis, *Am. J. M. Sc.* **211**:571 (May) 1946.

22. Babin, F., and Dulaney, A. D.: Complement Fixation in Malaria and Syphilis, *Am. J. Hyg.* **42**:167 (Sept.) 1945.

a phosphate buffer extract of *Plasmodium knowlesi*. Quantitative serologic tests for both syphilis and malaria were performed on specimens of serum from 22 syphilitic patients under treatment with inoculation malaria. In all cases, the reaction to the complement fixation test for malaria became positive, the titer paralleling the parasite count. Eighteen (82 per cent) of the patients also showed a rise in Wassermann titer coincident with and in proportion to the degree of positivity observed with the complement fixation test for malaria. The nature of the inter-reactivity observed in the complement fixation tests for syphilis and malaria has not been established, but these authors suggest two possible explanations: (1) that there is a common or closely related antigenic component in the antigens which are responsible for the cross reaction and (2) that malaria activates syphilitic infections, the increased titer of serologic tests for syphilis occurring during malaria representing an anamnestic reaction.

Robinson and McKinney²³ have performed tests on the blood serum for syphilis and have examined the spinal fluids of 100 non-syphilitic white men with *Plasmodium vivax* malaria. Weekly tests of the blood were done on all patients with positive or doubtful reactions to Kahn tests until seronegativity was reestablished. Positive reactions to tests of the blood were found in 35 per cent of this group of patients, and an additional 11 per cent had doubtful reactions. There was no apparent correlation between the number of attacks of *P. vivax* malaria and the development of biologic false positive reactions to serologic tests for syphilis. The majority of positive reactors were seronegative within four weeks and all by the end of eleven weeks. Of especial interest is their negative report so far as the spinal fluid is concerned. In no instance was the spinal fluid cell count elevated, nor were there any positive Kahn reactions of the spinal fluid.

Tuberculosis.—The results of a study of 100 infants with various serious manifestations of tuberculosis in relation to occurrence of false positive serologic reactions for syphilis are reported by Sellek Azzi and del Frade.²⁴ Falsely positive reactions for syphilis were obtained in from 3 to 4 per cent of these tuberculous infants. Of special interest is the fact that 18 per cent of 50 patients with tuberculous meningitis had false positive reactions to tests of the spinal fluid for syphilis.

Infections of the Respiratory Tract.—Florman and Weiss²⁵ have examined serial specimens of serum from 68 patients with a clinical

23. Robinson, H. M., Jr., and McKinney, W. W.: *Vivax Malaria and Serologic Tests for Syphilis*, J. A. M. A. **129**:667 (Nov. 3) 1945.

24. Sellek Azzi, A., and del Frade, A.: *Porcentaje y naturaleza de las reacciones falsas positivas de sífilis en tuberculosis*, Bol. Soc. cubana de pediat. **17**: 159 (May) 1945.

diagnosis of primary atypical pneumonia for the presence of four different antibodies: cold agglutinins, indifferent streptococcus agglutinins, elementary body type virus complement-fixing antibodies and reagin, the reacting substance in serodiagnostic tests for syphilis. Six of 36 patients tested (17 per cent) had transiently positive serologic reactions for syphilis during convalescence from primary atypical pneumonia. Six other patients had transiently doubtful reactions. There was no apparent correlation between the occurrence of other positive reactions (cold agglutinins, streptococcus agglutinins or elementary body virus antibodies) and the occurrence of biologic false positive serologic reactions for syphilis.

Lymphogranuloma Venereum.—The occurrence of biologic false positive reactions to serologic tests for syphilis in certain cases of lymphogranuloma venereum has been described. The hyperproteinemia associated with this condition has been suggested, but never proved, to be the cause. Heymann and Webb²⁶ have studied in 25 patients with proved lymphogranuloma venereum the results of serologic reactions for syphilis, formol-gel reactions and determinations of serum protein. Thirteen patients had concomitant syphilis, and, of the remaining 12, there were 3 with biologic false positive serologic reactions. There was no correlation between the occurrence of false positive reactions and hyperproteinemia. They appeared to be related to the activity of the lymphogranuloma venereum infection and usually persisted from two to three weeks, reverting to negative as the bubos healed.

Chickenpox.—Kane and Henneman²⁷ have added chickenpox to the list of the conditions which may produce biologic false positive reactions to serologic tests for syphilis. Among 22 patients with chickenpox, five transiently positive reactions to Hinton flocculations tests were observed, 1 of the patients also having a transiently positive Kahn reaction. In no case was the reaction to the Wassermann complement fixation test positive. All but 1 of the patients in whom positive reaction to Hinton tests developed were young college students, in whom there was no reason to suspect syphilis. The earliest positive reaction developed seven days after the onset of the eruption and in 1 case persisted for fifty-one days. This series is too small to reflect the true incidence of biologic false positive reactions in chickenpox, but the findings suggest that they are not infrequent, at least with the Hinton modification of the flocculation test.

25. Florman, A. L., and Weiss, A. B.: Serologic Reactions in Atypical Pneumonia, *J. Lab. & Clin. Med.* **30**:902 (Nov.) 1945.

26. Heymann, A., and Webb, E. L.: False Positive Serologic Reactions for Syphilis in Lymphogranuloma Venereum, *J. Ven. Dis. Inform.* **27**:122 (May) 1946.

27. Kane, L. W., and Henneman, P. H.: False-Positive Hinton Reactions Following Chicken Pox, *New England J. Med.* **233**:407 (Oct. 4) 1945.

Erythema Nodosum.—Löfgren²⁸ suggests that biologic false positive serologic reactions for syphilis may occur in association with erythema nodosum. The cases described were part of a larger series being studied from the standpoint of etiology and pathogenesis of erythema nodosum. Among 178 patients, there were 7 with positive serologic reactions for syphilis considered to be nonspecific.

Seroresistance.

So frequently is the consultant syphilologist called on to explain to the patient (and all too often to his doctor as well) the phenomenon of persistent seropositivity that Moore²⁹ has recorded in dialogue form an imaginary conversation between a seroresistant patient and his physician, deliberately so designed that reprints of the article may be handed to patients and sent to their family physicians in order to supplement the lengthy interviews and the equally lengthy letters which now are so necessary. The printed word never can replace the personal contact between physician and patient, though it is believed that a preliminary reading of this discussion by a worried seroresistant patient will form the basis for a more satisfactory and individualized consultation. Physicians occasionally faced with the problem of persistently positive reactions to serologic tests following adequate therapy for late (especially latent) syphilis will find this discussion well worth reading. Consultant syphilologists may well utilize this device or some modification of it based on their own experience as a time-saving and effective educational expedient.

CLINICAL MANIFESTATIONS

Early Syphilis.

Primary Lesions.—As Tello³⁰ points out, the frequency of asymptomatic infections in women is more apparent than real, becoming less frequent as greater care is used in examination, especially of the cervix. Chancre of the cervix must be sought to be identified. These lesions, according to the author, may be superficial erosions, deeper ulcerations or vegetating lesions. Cervical secretions or menstrual blood may contain the spirochetes of syphilis either in the presence or in the absence of visible lesions.

Hazen³¹ has contrasted the Negro and white races in respect to the incidence of extragenital syphilitic infection. In his experience, only

28. Löfgren, S.: False Positive Seroreactions for Syphilis in Connection with Erythema Nodosum, *Acta dermat-venereol.* **26**:243 (Jan.) 1946.

29. Moore, J. E.: Seroresistance (Wassermann-Fastness) in Syphilis: A Discussion for the Patient, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:125 (March) 1946.

30. Tello, E. E.: *Sífilis primaria de cuello de útero en la mujer no embarazada*, Thesis for the Doctorate, Cordoba, University of Cordoba, 1945.

31. Hazen, H. H.: Extragenital Syphilitic Infection in Negroes, *Arch. Dermat. & Syph.* **52**:114 (Aug.) 1945.

19 of 3,700 Negro patients with early syphilis had extragenital chancres, a percentage of 0.51. This is about 1/10 the reported percentage among white patients.

- *Electrocardiographic Changes in Early Syphilis.*—Whether the spirochetes which lodge in the cardiac muscle during the spirochetemia of early syphilis cause any demonstrable alteration in cardiac function has been the subject of conflicting opinions. Klotz and Crede³² found definite electrocardiographic changes (abnormally shaped T waves) in 4 of 100 patients with early syphilis, which became normal after a twenty day course of arsenotherapy. Six additional patients showed low voltage T waves, which increased in amplitude following the completion of treatment. Other findings noted in isolated instances were low voltage with some slurring of the initial complexes, slight depression of the S-T segments, ectopic ventricular premature systoles and a shifting pacemaker, all of which disappeared following therapy. The authors feel that the electrocardiographic changes observed indicate that myocardial damage may occur in early syphilis.

Relapse and Reinfection.

As Moore³³ states editorially in the *American Journal of Syphilis, Gonorrhea and Venereal Diseases*, the problems of reinfection, superinfection and relapse have assumed far greater importance since the advent of intensive arsenical and penicillin therapy. Even with rigid criteria, reinfection appears now to be from five to ten times as common as in previous years. In a critical analysis, it is pointed out that newer methods of treatment have made invalid several of the previously proposed criteria of reinfection, leaving little evidence on which to differentiate among reinfection, superinfection and infectious relapse, save alone clinical "impressions" or diagnostic "hunches," which do not constitute proof. There are reasons, based primarily on experimentation with animals but also on recent clinical observations, to discard the concept that reinfection is proof of cure. If this concept is incorrect, superinfections and reinfections may well be more frequent than is commonly supposed. To the individual patient, the subject is of academic interest only, since whether he is reinfected, superinfected or relapses he must be retreated. To physicians attempting to evaluate accurately new and rapidly effective schedules of treatment, it is of practical importance. As more precise methods of effecting a differentia-

32. Klotz, S. D., and Crede, R. H.: Electrocardiographic Changes in Early Syphilis Prior to and upon Completion of Intensive Arsenotherapy, *Am. Heart J.* 30:551 (Dec.) 1945.

33. Moore, J. E.: The Changing Concept of Reinfection with Syphilis and Its Applicability as a Criterion of Cure, editorial, *Am. J. Syph., Gonorr. & Ven. Dis.* 29:474 (July) 1945.

tion are lacking, it is unfortunately necessary to designate all supposed reinfections as "treatment failures."

Noting that wholesale reports of so-called reinfections have followed the introduction into syphilotherapy of new and supposedly "curative" procedures, Beerman³⁴ enjoins caution in relaxing the rigidity of criteria for proof of reinfection. He bases much of his discussion on an extensive review of the literature pertaining to the problem of human reinoculations with *T. pallidum*. Thomas, Wexler and Schur³⁵ have observed a patient with cardiovascular syphilis (aortic regurgitation) in whom, having been treated to the point of seronegativity, there developed ten years after treatment for his original infection a dark field-positive chancre of "superinfection." The alternate explanation is, of course, that after cure of the original infection and gradual dissolution of whatever immunity it may have engendered the patient was reinfected.

Ocular Syphilis.

Interstitial Keratitis.—Woods and Chesney³⁶ summarize the results of an extensive series of experiments on the relation of the eye to immunity to syphilis, in which they found that (a) the corneas of rabbits with experimental syphilis induced by intratesticular inoculation do not always share in the immunity to reinfection which develops during the course of syphilitic infections; (b) direct inoculation of the cornea is followed by the development in that tissue of a local resistant state, although in some instances the protection thus conferred either is not absolute or is not permanent, and (c) vascularization of the cornea appears to be a factor in influencing favorably the development of a local resistant state.

The authors discuss the bearing of their findings on the pathogenesis of interstitial keratitis. It is suggested that the usual late occurrence of the lesions of interstitial keratitis may be due to a combination of lack of local immunity in the cornea in some cases of congenital syphilis plus the occurrence of minor traumatic incidents as the initiating factor. The fact that the lesions of interstitial keratitis may heal spontaneously as vascularization occurs may be explained on the basis of the development of a local immunity, presumably through antibodies

34. Beerman, H.: The Problem of Reinoculation of Human Beings with *Spirochaeta Pallida*: A Review of the Literature, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:173 (March) 1946.

35. Thomas, E. W.; Wexler, G., and Schur, M.: Report of a Chancre Developing in a Patient with Cardiovascular Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **29**:604 (Nov.) 1945.

36. Woods, A. C., and Chesney, A. M.: Relation of the Eye to Immunity in Syphilis with Special Reference to the Pathogenesis of Interstitial Keratitis, *Am. J. Ophth.* **29**:389 (April) 1946.

present in the blood. The tendency of the lesions of interstitial keratitis to recur may be related to the fading of a local immunity.

Syphilitic Uveitis.—The difficulties in establishing the diagnosis of syphilitic uveitis and in evaluating the results of therapy are discussed by Klauder and Dublin,³⁷ who report a series of 72 cases. These authors point out that neither clinical appearances, positive serologic reactions for syphilis, occurrences of Herxheimer reactions nor responses to anti-syphilitic treatment are infallible criteria in the diagnosis of syphilitic uveitis. Clinically there are no features of serous or plastic iritis pathognomonic of syphilis. The nodular type, while somewhat more characteristic, may be confused with iritis due to such other causes as tuberculosis, sympathetic ophthalmitis, sarcoidosis, leukemia, leprosy and neoplasm. The occurrence of Herxheimer reactions was studied with the corneal microscope and the slit lamp before and after therapy. This reaction was observed in 70 per cent of 65 patients with early syphilitic uveitis and in all of 7 patients whose only other evidence of syphilis was a positive serologic reaction. Since, however, 9 of 36 patients (25 per cent) with uveitis unassociated with clinical evidence of syphilis also had transient intensification of the inflammatory reactions following therapy, the authors do not believe that the occurrence of a Herxheimer reaction following therapy constitutes an absolute criterion in differential diagnosis.

The therapeutic response of syphilitic uveitis was good. Not only did the acute inflammation subside, but visual acuity seemed fairly well preserved. In only 1 patient was the outcome inadequate for industrially useful vision. Secondary glaucoma occurred in 3 cases. Seventeen patients with uveitis associated with early syphilis were treated with penicillin in a total dosage of 2,400,000 units. Penicillin had a prompt effect on the ocular lesion. Inflammation disappeared in from eight to fourteen days after the first injection in all but 2 patients, and no ocular relapse was observed during the period of observation.

The authors point out, however, that antisyphilitic treatment may exert a nonspecific effect on inflammatory processes of the uveal tract. Furthermore, syphilitic iritis may heal in the absence of treatment. In the authors' experiences, the beneficial nonspecific effect of anti-syphilitic treatment was not uniform nor was it always lasting. Since a definite diagnosis of syphilitic uveitis cannot be made clinically and since histologic examination or dark field demonstration of *T. pallidum* is not feasible, Klauder and Dublin state the belief that the diagnosis is established by evaluating all available data, the most important criteria

37. Klauder, J. V., and Dublin, G. J.: Syphilitic Uveitis: Diagnosis, Herxheimer Reaction and Results of Various Treatments, Including Penicillin Therapy, *Arch. Ophth.* **35**:384 (April) 1946.

being (1) evidence of recent infection with syphilis, (2) the exclusion of other possible etiologic factors and (3) a prompt response to antisymphilitic treatment.

Aural Syphilis.

Rodger³⁸ has recorded his observations on aural syphilis, drawn from 500 cases of syphilis involving the ears, nose and throat. His speculations as to the site of the lesion in the various types of deafness occurring in congenital and acquired syphilis are undocumented by pathologic evidence; his statement that syphilis causes diseases of the middle ear will not be accepted by most experienced otologists and syphilologists, and his discussion of the results of treatment in syphilitic cochlear and vestibular disease is worthless.

Cardiovascular Syphilis.

Uncomplicated Aortitis.—The successful clinical diagnosis of uncomplicated syphilitic aortitis depends on the alertness and clinical acumen of the examiner as well as the extent of the pathologic process. That this condition frequently is overlooked is readily apparent from the discrepancy between its incidence in clinical and pathologic reports. Dressler³⁹ has studied 1,270 patients with syphilis in an effort to seek criteria that permit a diagnosis of uncomplicated aortitis. In this series, a clinical diagnosis of cardiovascular syphilis was made in 30.7 per cent of the cases. Of the patients with conditions so diagnosed, 78 per cent were considered to have uncomplicated aortitis. To the author, the results of his study suggest that uncomplicated aortitis is a symptomless condition. The following criteria are suggested for establishing a diagnosis of aortitis in patients under 40 years of age: (1) the presence of a typical aortic second sound, (2) suprasternal pulsations, (3) increased paramanubrial dulness in the second intercostal space, (4) hypertension and (5) fluoroscopic evidence of aortic dilatation.

Aneurysms of the Thoracic Aorta.—Uncomplicated syphilitic aneurysm of the thoracic aorta imposes little or no appreciable strain on the heart. When congestive cardiac failure supervenes, it is oftenest the result of involvement of the aortic valve or of narrowing of the coronary ostiums. In either instance, the strain is predominantly on the left ventricle.

A rarer complication of aortic aneurysm, discussed by Brill and Jones,⁴⁰ is compression of the pulmonary artery, with or without arterio-

38. Rodger, T. R.: Aural Syphilis, *Brit. J. Ven. Dis.* **21**:115 (Sept.) 1945.

39. Dressler, M.: Cardiovascular Syphilis: An Approach to Early Clinical Recognition and Early Treatment, *Connecticut M. J.* **9**:844 (Nov.) 1945.

40. Brill, I. C., and Jones, R. S.: The Syndrome of Compression of the Pulmonary Artery by a Syphilitic Aortic Aneurysm With or Without Arterio-Arterial Communication, *Ann. Int. Med.* **24**:111 (Jan.) 1946.

arterial communication. In this instance, the strain is predominantly on the right ventricle. The authors suggest that when severe cardiac failure on the right side supervenes in a case of syphilitic aneurysm of the thoracic aorta without other discernible complications to account for the congestive failure compression of the pulmonary artery should be suspected. Arterioarterial communication is indicated by the presence of a continuous machinery type of murmur in the area of the pulmonary valve similar to that frequently observed in patent ductus Botalli.

A number of procedures have been advocated for producing occlusion of large blood vessels. In addition to the ineffectual results and fatal complications that attend many of these methods almost all are too traumatic for application to a thin-walled syphilitic aneurysm of the aorta. The methods of occlusion may be classified as follows: (1) the insertion of foreign bodies into the lumen of the vessels to produce thrombosis (Blakemore⁴¹), (2) external compression of the vessel and (3) injuries to the wall of the vessel, resulting in fibrosis and constriction of the lumen.

Poppe and de Oliveira⁴² report the successful use of applications of polythene cellophane to fibrous and obliterate syphilitic aneurysms of the thoracic aorta. Preliminary experimental data indicated that polythene cellophane was superior to other types and that the method was surgically feasible in dogs. The authors have successfully treated aneurysms of the aorta and have obliterated a patent ductus arteriosus by the method.

Neurosyphilis.

Asymptomatic Neurosyphilis.—Merritt⁴³ found asymptomatic neurosyphilis to be present in 9.5 per cent of 2,263 patients with syphilis of five or more years' duration. An analysis of 676 cases of neurosyphilis of all types showed that asymptomatic neurosyphilis constituted 32 per cent of the total. The latter group of 200 cases of asymptomatic neurosyphilis is discussed in detail. In 8 per cent of the 200 patients there developed clinical evidence of progression following therapy. In no patient with minimal pretreatment abnormalities of the spinal fluid did the condition progress to parenchymatous neurosyphilis, and in only 4 per cent did lesions of the meningovascular type develop. On the other hand, parenchymatous neurosyphilis developed in 20 per cent of the patients with fluids of the group III type.

41. Blakemore, A. H.: *Electrothermic Coagulation of Aneurysms*, in Nelson Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1945, chap. 12-B.

42. Poppe, J. K., and de Oliveira, H. R.: *Treatment of Syphilitic Aneurysms by Cellophane Wrapping*, *J. Thoracic Surg.* **15**:186 (June) 1946.

43. Merritt, H. H.: *Asymptomatic Neurosyphilis*, *Clinics* **4**:475 (Aug.) 1945.

Dementia Paralytica (Palmomental Reflex in).—Thompson ⁴⁴ reports that the palmomental reflex has a high degree of specificity in dementia paralytica, is one of the first physical signs to appear and is present "in almost 100 per cent of cases of this disorder." The palmomental reflex is elicited by stroking with a moderately sharp instrument the thenar eminence from the base of the thumb to the wrist. As the stroke is made, the examiner watches the ipsilateral side of the patient's chin. A positive sign is elicited when the skin just lateral to the midline of the chin forms a dimple and moves laterally and upward. The sign oftenest is ipsilateral, but it may be contralateral and occasionally bilateral. The significance of the sign is its frequency of occurrence in diseases causing diffuse cortical damage. A positive palmomental sign occurs in about 2 to 3 per cent of normal persons. Among the diseases in which the sign occurs are multiple sclerosis, lethargic encephalitis, other forms of neurosyphilis, cerebral arteriosclerosis, severe alcoholic mental deterioration and opium addiction with mental deterioration. In none of these is it as consistently present as in dementia paralytica.

Syphilitic Amyotrophy.—So common is muscular atrophy in the course of tabes dorsalis that it is generally accepted as one of the predominant signs of the condition. Extremely controversial, however, is the relationship of syphilis to neurologic syndromes such as chronic poliomyelitis, amyotrophic lateral sclerosis and the muscular dystrophies.

Revilla ⁴⁵ describes 7 patients with syphilis in whom the outstanding objective findings were those of amyotrophy and in whom he believes the etiologic factor was syphilis. Pain was a predominant symptom, in contrast to idiopathic amyotrophic lateral sclerosis, which ordinarily is painless. Certain other clinical differences were observed: the muscular atrophy was asymmetric and irregular in distribution; deep reflexes usually were hypoactive, although occasionally hyperactive; pupillary abnormalities were frequent, and the clinical course was more protracted and less consistently progressive than that in the idiopathic type of amyotrophy.

Antisyphilitic therapy appears to influence the course of the muscular dystrophy but little. Even fever therapy is ineffectual, reports Vraa-Jensen,⁴⁶ who has treated 6 patients with "amyotrophic cerebrospinal syphilis" with the Kettering hypertherm.

Avitaminosis and Syphilis of the Spinal Cord.—In recent years there has been considerable investigation of the neuropathologic changes pro-

44. Thompson, G. N.: The Palmo-Mental Sign, *Bull. Los Angeles Neurol. Soc.* **10**:174 (Sept.-Dec.) 1945.

45. Revilla, A. G.: Syphilitic Amyotrophy: Clinical Study of Seven Cases, *Dis. Nerv. System* **7**:69 (March) 1946.

46. Vraa-Jensen, G.: Amyotrophic Cerebrospinal Syphilis, *Acta psychiat. et neurol.* **21**:795, 1946.

duced by avitaminosis. Shulack and Peters' review⁴⁷ of the present status of these investigations reveals degeneration of the posterior columns of the spinal cord to be the commonest manifestation of long-standing vitamin deficiency. Less often the lateral columns show degenerative changes.

Heilbrunn and Hoffenberg⁴⁸ have treated 15 patients with various neurologic disorders with oral administration of vitamin B complex and vitamin E and intrathecal injection of crystalline thiamine hydrochloride. Included in the group were 3 patients with tabes dorsalis, 2 of whom showed symptomatic improvement (in ataxia and sensory disturbances).

Electroencephalograms in Neurosyphilis.—Greenblatt and Levin⁴⁹ have found electroencephalographic abnormalities in 50 per cent of 233 cases of neurosyphilis. The incidence of abnormality in the various clinical types was meningovascular neurosyphilis, 60 per cent; dementia paralytica, 55 per cent, and tabes dorsalis, 14 per cent. In a control group, the incidence of abnormality was 10 per cent.

Twenty per cent of the patients with neurosyphilis had histories of convulsive attacks. The highest incidence of convulsions was among patients with meningovascular involvement, attacks also being common among those with dementia paralytica. Abnormal electroencephalograms were especially frequent among patients with a history of seizures.

In the group of persons with dementia paralytica, various clinical and laboratory findings were correlated with the incidence of abnormality of electroencephalograms. The presence of tremors, dysarthria and other somatic signs raised the incidence of electroencephalographic abnormality. The degree of spinal fluid abnormality and the presence of evidence of "activity" showed a slightly positive correlation. No correlation was apparent between electroencephalographic abnormality and pupillary changes or the presence of delusions or hallucinations. Of considerable interest is the finding that electroencephalographic abnormalities are frequent in cases of primary optic atrophy. This unexplained observation has previously been reported.⁵⁰

In the neurosyphilis clinics of the Boston Psychopathic Hospital,⁵¹ 44 of 223 patients with heterogeneous syphilis of the nervous system

47. Shulack, N. R., and Peters, M.: Spinal Cord Changes with Avitaminosis, J. Nerv. & Ment. Dis. **102**:359 (Oct.) 1945.

48. Heilbrunn, G., and Hoffenberg, N.: Intrathecal and Oral Vitamin Therapy in Various Neurologic Disorders, J. Nerv. & Ment. Dis. **102**:379 (Oct.) 1945.

49. Greenblatt, M., and Levin, S.: Factors Affecting the Electroencephalogram of Patients with Neurosyphilis, Am. J. Psychiat. **102**:40 (July) 1945.

50. Finley, K. H.; Rose, A. S., and Solomon, H. C.: Electroencephalographic Studies on Neurosyphilis, Arch. Neurol. & Psychiat. **47**:718 (May) 1943.

51. Greenblatt, M., and Levin, S.: Neurosyphilis, Convulsions and Electroencephalography, Urol. & Cutan. Rev. **50**:331 (June) 1946.

were known to have had epileptiform attacks. Of these patients 35 had dementia paralytica, and the remaining 9 had meningovascular neurosyphilis. Grand mal seizures were predominant, although focal convulsions were commoner in cases of meningovascular disease. There were no instances of petit mal. Approximately half of these 223 patients had electroencephalographic abnormalities, and the authors claim a correlation of these abnormalities with the incidence of epileptiform attacks. In their experience, the more abnormal the electroencephalogram, the greater the likelihood of the patient's having a history of convulsions. In a comparison of seizures in cases of neurosyphilis with seizures to the "general population," it was found that there is a greater number of slow wave abnormalities among the patients with neurosyphilis than among patients with so-called idiopathic epilepsy.

Abnormalities of Spinal Fluid.—The spinal fluid syndrome characterized by a negative Wassermann reaction and "first zone" colloidal reaction is found, according to Rouquès,⁵² almost invariably in cysticercosis and trypanosomiasis, not infrequently in multiple sclerosis but only rarely in neurosyphilis.

Lumbar Puncture.—Following lumbar puncture there may occur a syndrome consisting of headache, varying in intensity and duration, nausea, vertigo, backache and stiffness of the neck. Characteristically, the headache is relieved by recumbency and aggravated by activity. The mechanism of this postpuncture reaction has been extensively discussed but never completely elucidated.

In Underwood's⁵³ experience, lumbar puncture was followed by temporarily incapacitating headache in 19 per cent of 500 cases. Postpuncture reactions were more frequent among patients whose spinal fluids were normal than among those with neurosyphilis. Other predisposing factors appeared to be initially low spinal fluid pressure, emotional reactions to the examination and a history of previous reactions to the procedure. Rest in bed following a lumbar puncture did not reduce the incidence of headache. Indeed, the evidence presented suggests that postpuncture recumbency increases not only its frequency but also its duration. Fifteen per cent of the group who did not rest and 25 per cent of those who rested after the procedure had moderate to severe reactions. Among those who returned to work immediately and in whom symptoms developed, 56 per cent of the headaches lasted three to five days; whereas in the group who remained recumbent, 60 per cent persisted three to seven days. Severe reactions lasted more

52. Rouquès, L.: Des réactions du Benjoin colloïdal et de Wassermann dans le liquide céphalo-rachidien, *Presse méd.* **54**:427 (June 29) 1946.

53. Underwood, L. J.: Lumbar Puncture Headache: A Statistical Analysis of Five Hundred Punctures, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:264 (May) 1946.

than three days in '97 per cent and longer than five days in 36 per cent of the cases. One severe headache persisted for over six weeks. For extreme postpuncture reactions, rest in bed for twenty-four to forty-eight hours and the use of caffeine and sodium benzoate intravenously are recommended.

In their report of the use of sodium nicotinate given intravenously in the treatment of various types of headache, Goldzieher and Popkin⁵⁴ record that complete relief was afforded each of 13 patients with post-lumbar puncture headache. The dosage given was 100 mg. of nicotinic acid or its equivalent as the sodium salt. This form of therapy was not without discomfort, for the injections were followed by a "burning" sensation and flushing, restlessness, oppression and paresthesias. The relief of headache appeared to be correlated with the degree of peripheral flush.

Lumbar puncture as a diagnostic procedure seldom is attended by any untoward sequelae other than headache, but in rare instances neurogenic disturbances may occur. Robinson⁵⁵ has reported transient paralysis of the abducens nerve five days following this procedure. Rangell and Glassman⁵⁶ add acute spinal epidural abscess to the list of possible complications following routine lumbar puncture. This, which fortunately is extremely rare, usually consists in the following sequence of events: (1) severe pain in the root, the distribution depending on the level of the lesion; (2) a latent period, usually four to nine days in duration, followed by signs of compression of the spinal cord; (3) evidence of cord involvement, manifested by motor paralyses, hypesthesia and sphincter disturbances; (4) fever, tachycardia, leukocytosis and other signs of severe infection, and (5) localized tenderness and rigidity of the spine, with obvious inflammation of the paravertebral muscles and soft tissues. The epidural space is composed of a mesh-work of fatty and loose areolar tissue. It is oftenest infected via the hematogenous route but may be involved as a result of a direct extension from contiguous disease. The staphylococcus usually is the causative bacterium. Adequate surgical evacuation of the pus and open drainage are advised.

The Pathology of Syphilis.

In a continuation of his critical and statistical analysis of histopathologic changes in syphilis, Rosahn⁵⁷ compares two groups of patients

54. Goldzieher, J. W., and Popkin, G. L.: Treatment of Headache with Intravenous Sodium Nicotinate, *J. A. M. A.* **131**:103 (May 11) 1946.

55. Robinson, H. J., Jr.: Abducens Palsy (with Subsequent Recovery) Following Lumbar Puncture, *Am. J. Syph., Gonorr. & Ven. Dis.* **29**:422 (July) 1945.

56. Rangell, L., and Glassman, F.: Acute Spinal Epidural Abscess as a Complication of Lumbar Puncture, *J. Nerv. & Ment. Dis.* **102**:8 (July) 1945.

with syphilis, those seronegative and those seropositive, as to the frequency of fibrosis and round cell infiltration, described by Warthin as pathognomonic of syphilitic infection. The incidence of these lesions in the heart, pancreas, adrenal, liver and testis was not significantly different in the two groups. Moreover, syphilitic patients with typical "Warthin lesions" in multiple organs were no more likely to present positive serodiagnostic reactions than those with similar lesions in only one organ. The findings indicate that the changes described by Warthin are not related to the serum reactivity to serologic tests for syphilis.

Studying the bone marrow in 40 cases of syphilis, Dulanto Escofet⁵⁸ found evidence of a shift to the left in the myelocytic series and an increase in cells of the reticuloendothelial series. A close parallelism between serum globulin fractions associated with reagin formation and the number of plasma cells in the marrow was noted.

The Prognosis of Syphilis.

Information has long been sought concerning the effect of syphilis on the life expectancy of the infected person and the influence of treatment in improving the prognosis as to life expectancy.

As Schamberg⁵⁹ points out in an extensive critical review of the available clinical, postmortem and actuarial studies, four methods of study of the prognosis of syphilis have been used: (1) analysis of governmental mortality reports, (2) clinical studies, (3) death and autopsy studies and (4) life insurance studies. Older studies were found to be untrustworthy because of factors of selection and the inclusion of conditions now known to be unrelated to syphilis. In addition, the relative ineffectiveness of older forms of therapy and the general lack of treatment facilities make invalid conclusions reached in the past, when modern forms of treatment were not available.

Analyses of governmental mortality reports are unacceptable even as gross approximations; clinical studies ordinarily are weighted to an unknown but probably considerable extent with patients with serious late lesions whose life expectancy already is foreshortened, and post-mortem studies miss many cases in which the lesions have healed. In studies of American life insurance, the increased prevalence of syphilis in lower socioeconomic groups with a higher death rate introduces the major distortion. Misstatements on death certificates, inaccurate criteria

57. Rosahn, P. D.: Studies in Syphilis: VI. Fibrosis and Round Cell Infiltration of the Parenchymatous Organs (Warthin) in Relation to Serodiagnostic Findings, *J. Ven. Dis. Inform.* **27**:126 (May) 1946.

58. Dulanto Escofet, F.: El mielograma en la sífilis, *An. méd. de Barcelona* **32**:531 (Dec.) 1945.

59. Schamberg, I. L.: The Prognosis of Syphilis, *Am. J. Syph., Gonor. & Ven. Dis.* **29**:529 (Sept.) 1945.

of cure and adequacy of treatment and the effect of geographic residence are other factors.

The presumed increased mortality rate among syphilitic persons may be ascribed to two causes: (1) deaths directly resulting from syphilis, chiefly from late involvement of the cardiovascular and central nervous systems and occasionally as a result of treatment (since adequate early treatment prevents the serious late manifestations, deaths directly resulting from syphilis are inversely proportional to the adequacy of treatment) and (2) the higher mortality from all causes in socioeconomic, occupational and, in some cases, geographic groups in which syphilis is most prevalent.

Schamberg states the belief that, in view of the improving standards of present day diagnosis and treatment of syphilis and in view of the frequently benign character of the disease, life insurance companies could insure at standard rates the majority of syphilitic applicants for insurance without risk of increased death losses.

Even in view of the defects inherent in any analysis utilizing governmental mortality reports, it is possible to visualize, as has Usilton,⁶⁰ certain gross mortality trends in syphilis over a period of years. Utilizing data published by the Bureau of Census, this statistical analyst found that between 1939 and 1943 there were decreasing numbers of deaths reportedly "due to syphilis," and between 1910 and 1943 there were impressive declines in the number of deaths due to dementia paralytica and those due to tabes dorsalis. In the case of dementia paralytica, significant decline did not begin until 1923, a fact which may well be related to the fact that malaria therapy came into extensive use at about this time. Perhaps most striking is the progressive decline in the infant death rate over the ten year period 1933 to 1943.

The importance of maternal syphilis as a cause of premature delivery has been difficult to assess, because of several factors that influence the interpretation of the data. Among these are the amount of antisymphilitic therapy the patients have received and the possibility of coexistent diseases which also may induce premature labor. Brown, Lyon and Anderson⁶¹ have found, in the course of an extensive study of the causes of prematurity, that premature delivery occurred in approximately 5 per cent of mothers with normal pregnancies and in 10 per cent of those with syphilis. Antisyphilitic therapy administered during pregnancy significantly reduced the rate of prematurity.

60. Usilton, L. J.: Mortality Trends for Syphilis, *J. Ven. Dis. Inform.* **27**:47 (Feb.) 1946.

61. Brown, E. W.; Lyon, R. A., and Anderson, N. A.: Causes of Prematurity: V. Influence of Syphilis on the Incidence of Prematurity, *Am. J. Dis. Child.* **70**: 318 (Nov.-Dec.) 1945.

Heller and Bruyere ⁶² found that among Negro men between 25 and 50 years of age with untreated syphilis the life expectancy was about 20 per cent less than that among a comparable uninfected population. How significantly even a relatively small amount of antisyphilitic therapy may change the prognosis may be inferred by comparing this with Smith and Bruyere's ⁶³ results, which indicate that in a population of the same age, race and sex who were infected with syphilis and received "some" treatment the life expectancy was reduced only 10 to 12 per cent below that of the general population.

DRUGS: MERCURY, BISMUTH AND ARSENICAL

Mercury.

In modern syphilology, mercurial compounds have been abandoned. The usefulness of mercury now resides solely in the fact that the local application of ointment of mild mercurous chloride is still the most effective form of chemical prophylaxis. Fleming and Wolf ⁶⁴ have carried out an experiment with rabbits to evaluate the effect of particle size on the efficacy of ointment of mild mercurous chloride in the prophylaxis of syphilis. For this purpose three ointments containing mild mercurous chloride powder in particle sizes of 100 microns, 5 microns and 1 micron were used. Varying amounts of each of the three ointments were applied to the areas of inoculation one hour after standardized dark field-positive testicular emulsions had been rubbed into a superficial cutaneous scratch on each rabbit's back. Proof of protection or the lack of it was obtained by careful observation of the rabbits for chancre formation and, with clinically normal animals, by transfer of popliteal lymph nodes six months later. Their data show that greater protection was obtained with the ointments of smaller-sized particles, the particle size of 100 microns being relatively inefficacious.

Bismuth Preparations.

Vedrov ⁶⁵ points out that bismuth is best absorbed during the first course of treatment, before local tissue sclerosis and vascular thrombosis resulting from previous injections have occurred. How greatly

62. Heller, J. R., Jr., and Bruyere, P. T.: Untreated Syphilis in the Male Negro: II. Mortality During Twelve Years of Observation, *J. Ven. Dis. Inform.* **27**:34 (Feb.) 1946.

63. Smith, D. C., and Bruyere, M. C.: The Effect of Treated Acquired Syphilis on Life Expectancy, *J. Ven. Dis. Inform.* **27**:39 (Feb.) 1946.

64. Fleming, W. L., and Wolf, M. H.: The Relative Prophylactic Effectiveness Against Syphilis of Ointments Containing Calomel in Different Particle Size, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:47 (Jan.) 1946.

65. Vedrov, N. S.: Bismuth in the Treatment of Syphilis, *Am. Rev. Soviet Med.* **3**:106 (Dec.) 1945.

previous trauma interferes with absorption is indicated by an experiment on rabbits. A comparison was made of the bismuth content of muscles into which Biochinol (quinine bismuth iodide in peach kernel oil) was injected (*a*) one month after trauma produced by the injection of 1 cc. of pure peach kernel oil once every six days for eight injections and (*b*) when not previously traumatized. Approximately 70 per cent of the bismuth injected into undamaged muscles had been absorbed after a ten day period, while in the injured muscles the amount absorbed during the same period was only 34 per cent.

The author also studied in human patients the elimination of bismuth in urine (*a*) after one injection of Biochinol; (*b*) during one course of treatment and after its completion, and (*c*) during a repeated course of treatment and after its completion. There was a significant difference in the amount of bismuth excreted in the urine during the first course of therapy and during subsequent courses. Elimination during later series of treatment was 14 per cent of the amount injected, as compared with 32 per cent during the first course.

Arsenical Drugs.

In studying the trypanocidal and spirocheticidal activity of a series of acid-substituted phenyl arsenoxides, Eagle⁶⁶ was able to correlate therapeutic effectiveness with increasing hydrogen ion concentration within the pH range of 5.5 to 9.0. This was due to the fact that ionized salts of the various compounds were far less active than the undissoiated free acids, which had a uniform molar activity approximating that of unsubstituted phenyl arsenoxide. The relative ineffectiveness of the salts of the acid-substituted phenyl arsenoxides therefore reflects the fact that they are not bound by the organisms. Variations in pH , affecting the ion-free acid ratio, affected the degree to which a given arsenical was bound by the organisms.

Toxic Effects of Arsenical Compounds.—The most recent analyses of Navy reports⁶⁷ indicate how much less frequent are serious untoward reactions from oxophenarsine hydrochloride than from neoarsphenamine. In a twenty year period, 1,392,838 injections of neoarsphenamine have been given, with 1,034 reactions, including 54 fatalities reported, a ratio of 1 death to every 25,793 injections. With 1,006,951 injections of oxophenarsine hydrochloride, there have been 173 reactions.

66. Eagle, H.: The Spirocheticidal and Trypanocidal Action of Acid-Substituted Phenyl Arsenoxides as a Function of pH and Dissociation Constants, *J. Pharmacol. & Exper. Therap.* **85**:265 (Nov.) 1945.

67. Burton, O. L.; Justyn, G. W., and Anderson, L. T.: Toxic Effect of Arsenical Compounds, *U. S. Nav. M. Bull.* **45**:783 (Oct.) 1945; Toxic Effects of Arsenical Compounds, as Employed in the Treatment of Diseases in the United States Navy, 1944, *ibid.* **46**:139 (Jan.) 1946.

only 6 of which were fatal, a ratio of 1 death to every 167,825 injections. The six deaths due to oxophenarsine hydrochloride were two from toxic encephalopathy and one each from hepatic damage, acute renal damage, hemorrhagic encephalitis and circulatory collapse. Arsenical dermatitis was the most frequently reported reaction. These Navy data do not reflect the mortality rate from intensive arsenotherapy with either drug.

Blood dyscrasias following arsenical therapy are grave complications. Repeatedly described have been aplastic anemia, agranulocytosis and thrombocytopenia, all manifestations of depressed activity of bone marrow. The report of a case of Young, Valentine and Howland,⁶⁸ in which death followed the fifth injection of neoarsphenamine, indicates that acute hemolytic anemia also may occur as a complication of arsenical therapy and that hemolytic jaundice should be included among the possible causes of postarsenical icterus.

Larsen⁶⁹ states the belief that hemorrhagic encephalitis is due to an allergic reaction to arsenical therapy. To support his contention, he points out, among other things, that this reaction is of rare occurrence, that even small doses may evoke the complication, that most of these reactions occur early in the course of therapy and that histopathologic studies are constant with the hypothesis.

Colloidoclastic shock following the injection of oxophenarsine hydrochloride is rare. In Shapiro's⁷⁰ patient, treated for blastomycosis rather than for syphilis, there developed ashen pallor, apnea and circulatory collapse following the second injection. Recovery was prompt.

Conrad⁷¹ adds to the list of eruptions reported following the use of oxophenarsine hydrochloride a fixed dermatitis with pemphigoid features.

In reporting 2 cases of acute agranulocytosis, 1 with coexisting toxic hepatitis attributable to therapy with oxophenarsine hydrochloride, McManus⁷² indicates that penicillin was of distinct value both as prophylaxis against the usually fatal septicemia which commonly develops and as therapy for the underlying syphilitic infection.

68. Young, L. E.; Valentine, W. N., and Howland, J. W.: Acute Hemolytic Anemia Due to Neoarsphenamine: Report of a Fatal Case, *Ann. Int. Med.* **24**: 104 (Jan.) 1946.

69. Larsen, J. F.: Encephalopathia allergica e neosalvarsano, *Acta psychiat. et neurol.* **21**:473, 1946.

70. Shapiro, A. L.: Colloidoclastic Shock Following Injection of Oxophenarsine Hydrochloride (Marpharsen), *Arch. Dermat. & Syph.* **52**:395 (Nov.-Dec.) 1945.

71. Conrad, A. H., Jr.: Fixed Arsenical Eruption with Bulla Formation, *Bull. U. S. Army M. Dept.* **5**:726 (June) 1946.

72. McManus, J. F.: Agranulocytosis Following Mapharsen Therapy, *New England J. Med.* **234**:17' (Jan. 3) 1946.

Walsh and Wyatt⁷³ have observed the results of accidental intra-arterial injection of oxophenarsine hydrochloride. Severe pain distal to the point of injection, generalized in the forearm and hand but severest in the thenar and hypothenar eminences and in the finger tips, occurred immediately and persisted for several hours. There were no serious sequelae.

Leifer⁷⁴ stresses the danger of continued arsenotherapy in cases of "erythema of the ninth day." He reports 14 cases of this reaction occurring early in the course of arsenotherapy (from six to eleven days after the first injection). All patients had fever, headache and weakness, but only 3 had cutaneous eruptions. In all, early continuation of arsenical drugs after the initial reaction caused serious reactions, in the form of jaundice or agranulocytosis, each often accompanied with concomitant nephritis. The author expresses the opinion that the safest course is to consider any febrile episode (except the Herxheimer reaction) in the first three weeks of arsenotherapy as a probable manifestation of arsenical sensitivity.

Arsenical Jaundice and Syringe Hepatitis.—As a reaction to anti-syphilitic therapy, jaundice long has been considered unique. Its capricious occurrence (not infrequently late in the course of therapy), the facts that early resumption of arsenical therapy often is possible and that clinical differentiation from "catarrhal jaundice" is difficult and the lack of characteristic histopathologic changes in the liver all have reserved for this complication of antisyphilitic therapy a category unto itself.

It is now well recognized that hepatitis which may follow the injection of convalescent serum or of vaccines containing human serum is due to a hepatotoxic factor in the serum. This form of hepatitis, now known as "homologous serum jaundice," is indistinguishable from that which occasionally follows arsenotherapy, and there now is ample proof that in many cases "arsenical hepatitis" is in reality due to contamination of syringes with a transmissible icterogenic agent occasionally present in human serum. The problem has been the subject of several recent British publications, since in England the problem of "arsphenamine jaundice" long has been out of all proportion to the other toxic reactions associated with arsenical therapy. In a memorandum by medical officers of the British Ministry of Health⁷⁵ it is recommended that the technics of arsenical injection commonly used in England be revised. Theories that hepatitis is directly due to syphilis or that it is due to an

73. Walsh, E. N., and Wyatt, J. L.: Accidental Intra-Arterial Injection of Oxophenarsine Hydrochloride (Mapharsen), J. A. M. A. **129**:1255 (Dec. 29) 1945.

74. Leifer, W.: The Danger of Continued Arsenotherapy in Cases of Erythema of the Ninth Day, Am. J. M. Sc. **210**:458 (Oct.) 1945.

75. Role of Syringes in the Transmission of Jaundice, Lancet **2**:116 (July 28) 1945.

intercurrent infection spreading spontaneously among persons made unusually susceptible to the toxic effects of syphilis or of arsenic are rejected in view of conclusive evidence that an infective agent may be transmitted by syringes or needles.

In considering the prophylaxis of syringe hepatitis, Dalmady and Hardwick⁷⁶ stress that the quantity of icterogenic principle may be extremely small and that the agent is heat resistant and not killed by ordinary methods of sterilization. It is therefore believed essential that all syringes should be sterilized by dry heat. For routine chemical and serologic analysis, it is recommended that blood be withdrawn directly into collecting tubes, without the intermediary use of syringes.

Homologous serum jaundice has been reported following the parenteral (not necessarily intravenous) injection of insulin, gold, and bismuth preparations and acriflavine and even after the use of common syringes for venesection. As Howells and Kerr⁷⁷ point out, it also may follow injections of penicillin if proper precautions are not taken.

"BAL" Therapy of Arsenical Poisoning.—The compound dimercaprol ("BAL"; 2,3-dimercaptopropanol) was developed during the war as an antidote against arsenical blister gases. Subsequently, it was found also to be effective not only for local decontamination and treatment of the skin and eyes but also for systemic treatment of arsenic poisoning, either occurring after exposure to arsenical blister gases or observed as a complication of arsenotherapy. The brilliant experimental studies of Stocken, Thompson, Peters and their associates which led to the development of dimercaprol and the extensive studies of its biochemical and pharmacologic properties recently have been reviewed by Waters and Stock⁷⁸ and by Peters, Stocken and Thompson.⁷⁹

Eagle⁸⁰ summarizes the pharmacologic and clinical data which indicate that dimercaprol is of value in the treatment of certain types of arsenical poisoning. The toxicity of arsenicals rests on the fact that they combine with and block the function of physiologically essential chemical groupings in the cell, specifically of cellular sulfhydryl groups. Dimercaprol competes so favorably with sulfhydryl groups in the tissue that arsenic is removed from the cells even after being bound. A

76. Dalmady, E. M., and Hardwick, C.: Syringe-Transmitted Hepatitis, *Lancet* **2**:106 (July 28) 1945.

77. Howells, L., and Kerr, J. D. C.: Hepatitis After Penicillin Injections, *Lancet* **1**:51 (Jan. 12) 1946.

78. Waters, L. L., and Stock, C.: BAL (British Anti-Lewisite), *Science* **102**: 601 (Dec. 14) 1945.

79. Peters, R. A.; Stocken, L. A., and Thompson, R. H. S.: British Anti-Lewisite (BAL), *Nature, London* **156**:616 (Nov. 24) 1945.

80. Eagle, H.: The Systemic Treatment of Arsenic Poisoning with BAL (2,3-Dimercaptopropanol), *J. Ven. Dis. Inform.* **27**:114 (May) 1946.

regular and sometimes striking increase in arsenic excretion follows. Studies in animals poisoned by oxophenarsine hydrochloride, lewisite (betachlorovinylchloroarsine) or phenyl arsenoxide (arsenosobenzene) indicate that the widest margin of safety between toxic and effective doses of dimercaprol is provided by intramuscular injection (the drug dissolved in peanut oil) at four hour intervals. In human beings the therapeutic dose is approximately 3 mg. per kilogram, the number of injections depending on the severity of the complication. Larger doses may cause such untoward symptoms as nausea, vomiting, headache, a burning sensation in the lips, mouth, throat and eyes, myalgia and a sense of constriction in the chest. The results of systemic therapy with dimercaprol in cases of arsenic poisoning are summarized. Patients with toxic encephalitis, arsenical dermatitis and massive overdoses of oxophenarsine hydrochloride appear to have been benefited. In the severe complications the mortality rate apparently is reduced and the period of hospitalization shortened. In the milder complications, recovery is accelerated. The effect of dimercaprol in postarsenical blood dyscrasias and icterus is dubious. In all the reports, the importance of prompt administration of adequate amounts of dimercaprol is clearly evident.

In 55 patients with encephalopathy caused by intensive arsenotherapy, 40 were either convulsing or in coma at the time of administration of dimercaprol. Forty-four patients recovered within one to seven days, usually with improvement within one to three days; 11 died.

Eighty-eight patients with arsenical dermatitis have been treated, some systemically and some locally with dimercaprol ointments. The administration of dimercaprol usually stopped the progression of the inflammatory process. The average time for definite improvement to occur in exfoliative dermatitis was three days, and the average time for almost complete recovery was thirteen days.

In 10 of 11 cases of agranulocytosis due to arsenical therapy, administration of dimercaprol was followed by an increase in the white blood cell count and an even more striking increase in the proportion of polymorphonuclear granulocytes. The course of 3 patients with aplastic anemia was not influenced by dimercaprol in the doses used.

Three patients who were given massive overdoses of oxophenarsine hydrochloride and who received prompt and adequate amounts of dimercaprol recovered. A fourth patient received inadequate amounts of dimercaprol and died after an initially favorable response.

In 6 normal subjects, in 12 volunteers exposed to small concentrations of arsenical smoke and in 11 patients with arsenical dermatitis, the injection of dimercaprol regularly was followed by an increased urinary excretion of arsenic. This effect was relatively short lived, disappearing within four hours after a single injection.

Dimercaprol is itself toxic. This toxicity may be related to its strong reducing properties. It can destroy hemin or oxyhemoglobin by splitting the porphyrin ring and can also reduce methemoglobin or cytochrome C. Modified formulas of dimercaprol may be expected, and already a report by Danielli and his co-workers⁸¹ describes a glucoside of dithioglycerol ("BAL-Intra"), which may prove more suitable for systemic arsenical poisoning. Intravenous injections of this glucoside in dosage of 100 mg. per kilogram have been given without toxic symptoms, whereas doses of dimercaprol in excess of 4 mg. per kilogram have caused serious untoward reactions.

Intensive Arsenotherapy.—Bowman and Humphrey⁸² have treated 800 patients with early syphilis by the five day intravenous drip method. Their patients received oxophenarsine hydrochloride in total amounts from 1,000 to 1,200 mg., depending on body weight, and over 70 per cent also received intramuscular injections of thio-bismol. The outcome of treatment was considered satisfactory in 96.4 per cent of the cases of seronegative primary syphilis, in 83.9 per cent of the cases of seropositive primary syphilis and in 78.0 per cent of the cases of secondary syphilis. There were four deaths, a mortality ratio of one death in every 200 patients treated. Death was due to encephalopathy in 3 of the patients and to hepatic damage in the fourth. Three additional patients had severe but nonfatal encephalopathy.

However, Shaffer⁸³ reports that the five day intravenous drip method of massive arsenotherapy was abandoned because of serious reactions to treatment, results that were none too satisfactory and a lack of specially trained personnel. In its stead was substituted an ambulatory intensified treatment schedule consisting of a total of thirty injections of oxophenarsine hydrochloride and eight of bismuth subsalicylate given over a period of fifteen and two-thirds weeks. This is a compromise between the twenty-six week "Army" plan and the eight to ten week "Eagle" schedule. Two hundred and ten patients with early syphilis were assigned to this method of treatment during 1942.⁸³ The greatest drawback proved to be unsatisfactory case holding, since only 63 patients (30 per cent) completed the treatment with satisfactory regularity and remained under observation for six months or more.

81. Danielli, J. F.; Danielli, M.; Mitchell, P. D.; Owen, L. N., and Shaw, G.: Development of a Chemotherapy for Systemic Arsenical Poisoning, *Nature*, London **157**:217 (Feb. 23) 1946.

82. Bowman, G. W., and Humphrey, P. E.: Résumé of Eight Hundred Cases of Early Syphilis Treated by Five-Day, Slow-Drip Method, *J. Indiana M. A.* **38**:259 (Aug.) 1945.

83. Shaffer, L. W.: Intensive Arsenotherapy of Early Syphilis, *Arch. Dermat. & Syph.* **52**:147 (Sept.) 1945.

Of those who completed this form of therapy, 89 per cent had negative clinical and serologic results, 8 per cent were seroresistant and 3 per cent had clinical relapses. It was necessary to discontinue treatment in 7 cases because of reactions. Experiences with the eight week "Eagle" plan of intensified therapy are also given. A total of 352 patients were given three injections of oxophenarsine hydrochloride and one injection of bismuth subsalicylate per week for eight weeks. One hundred and ninety-four of these patients failed to complete this treatment. Among those whose therapy was completed there was a 10.3 per cent rate of failure (seroresistance, serorelapse or clinical relapse). Untoward reactions necessitated discontinuation of treatment for 8 patients.

Shaffer states the belief that such ambulatory intensive schedules are satisfactory for general use because of their safety, simplicity and effective results. The weakness of the method is the difficulty in holding patients to the schedule without lapses in treatment.

So acute has been the problem of lapses in the course of all but the most "intensified" of the treatment schedules that Trow and Dixon⁸⁴ have suggested that all patients be hospitalized during the entire treatment to insure its completion. However desirable this may be, it is not feasible. Hospital facilities are inadequate; the expense is too great, and social and business reasons make it impracticable to confine all patients to a hospital for antisyphilitic therapy.

Figueroa and Haraszti⁸⁵ have treated 1,000 patients with early syphilis by one of three schemes of intensive arsenotherapy. The five day intravenous drip method was used for 564 patients, and 500 (88.6 per cent) completed the treatment. Satisfactory results were obtained in 84.5 per cent of those whose therapy was completed. There were six deaths, all due to arsenical encephalopathy, a mortality rate of approximately 1 per cent. Of 186 patients treated by one of several thirty to forty day multiple syringe technics, 167 (89.8 per cent) completed treatment, with 79 per cent satisfactory results and no deaths. There were 250 patients treated by combined fever (from injections of foreign protein) and oxophenarsine hydrochloride, and 89.2 per cent completed the therapeutic course. The outcome was satisfactory in 93.8 per cent of the latter group. There were no deaths.

84. Trow, E. J., and Dixon, H. A.: Intensive Treatment of Early Syphilis with Oxophenarsine Hydrochloride by Multiple Injections, *Arch. Dermat. & Syph.* 52:155 (Sept.) 1945.

85. Figueroa, B. E., and Haraszti, S. E.: Experiencias sobre métodos modernos de arsenoterapia en 1000 casos de sífilis reciente, *Rev. med. e cir. de São Paulo* 19:3 (April) 1946.

Cannon's schedule of intensive arsenotherapy involving massive fractional doses of old arsphenamine administered by the syringe method three to four times daily over a period of from five to six days proved entirely unsuitable for the treatment of early syphilis. This die-hard attempt to retain for Erlich's "magic bullet" a place in modern syphilology has, however, enabled Cannon and his co-workers⁸⁶ to record some observations on blood and urinary levels of arsenic. The concentration of arsenic in the blood and urine was found to vary from patient to patient and from day to day throughout the period of treatment. Because of the prolonged presence of arsenic in the blood and urine following this method of administering arsphenamine, the suggestion is made that temporary retention of arsenical drugs by the body tissues may occur.

Krichevskaya and Lass⁸⁷ report finding arsenic in the cerebrospinal fluid in over half of a group of 92 patients who received massive arsenotherapy by continuous intravenous drip. Meningeal inflammation, increased body temperature and high concentration of arsenic in the blood are believed to be factors in facilitating the passage of arsenic through the hematoencephalic barrier.

Untoward Reactions to Intensive Arsenotherapy: Having treated 960 patients with the administration of oxophenarsine hydrochloride by the five day continuous drip method, Bowman and Humphrey⁸⁸ report twenty cerebral reactions, eleven of which were serious and five fatal. These reactions were more frequent in women, in the white race and among patients with florid secondary syphilis. Postmortem findings usually revealed cerebral edema rather than true hemorrhagic encephalopathy.

Polyneuritis is a rare complication of routine antisyphilitic therapy. It has been observed oftenest after treatment with sulfarsphenamine and commonly in association with exfoliative dermatitis. As Franks, Fetterman and Romano⁸⁹ point out, this complication has been more frequent since the introduction of more intensive methods of arsenotherapy.

86. Cannon, A. B.; Fisher, J. K.; Rodriguez, J. J.; Beattie, G. F., and Maechling, E. H.: Blood and Urine Arsenic Levels of Patients with Early Syphilis Under Intensive Arsenotherapy, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:144 (March) 1946.

87. Krichevskaya, E. I., and Lass, D. I.: Permeability of the Hemato-Encephalic Barrier in Massive Arsenotherapy, *Am. Rev. Soviet Med.* **3**:38 (Oct.) 1945.

88. Bowman, G. W., and Humphrey, P. E.: Cerebral Reaction Following Massive Five-Day Slow-Drip Syphilo-Therapy, *Urol. & Cutan. Rev.* **49**:557 (Sept.) 1945.

89. Franks, A. G.; Fetterman, J., and Romano, D.: Neurologic Manifestations During Arsenotherapy for Syphilis, *Urol. & Cutan. Rev.* **49**:681 (Nov.) 1945.

These authors state the belief that arsenical peripheral neuropathy may be limited to a single nerve and may occur in the absence of exfoliative dermatitis.

Since the occurrence of jaundice in association with the arsenotherapy of syphilis first was reported, the arsenical drugs have been regarded as potentially hepatotoxic. Impressed by the rarity of hepatitis among their patients treated by the intensive five day method of arsenoxide administration, Thomas and Olansky⁹⁰ have sought to determine the possible toxic effects of massive arsenotherapy on the liver. Forty-nine patients treated with an intensive schedule, involving the intravenous administration of 1,200 mg. of arsenoxide over a period of five days, were tested before and after therapy with the following tests of hepatic function: measurement of plasma protein levels, cephalin flocculation test, intravenous hippuric acid test and bromsulfalein test. In none did there develop abnormal hepatic function as measured by the plasma protein levels or the excretion of bromsulfalein. Results with the cephalin flocculation test in 34 of the 49 patients indicated pre-treatment subclinical hepatic damage, which usually improved following intensive antisyphilitic therapy. With the hippuric acid test, 37 per cent of the patients had abnormal hepatic function prior to therapy, and the post-treatment determinations again indicated not only the lack of further damage but actually the improvement of hepatic function. It is concluded that massive arsenotherapy does not usually produce hepatic damage. It also is suggested that in early syphilis there is active but subclinical hepatitis which responds favorably to antisyphilitic treatment.

Following the demonstration⁹¹ of the fact that reduction in the concentration of prothrombin in the blood occurs during massive arsenotherapy, Hoffman and Kalz⁹² have sought to correlate decreased prothrombin formation with impairment of other aspects of hepatic function. These investigators tested hepatic function by determining the blood prothrombin concentration, serum bilirubin levels, bromsulfalein retention and rate of hippuric acid synthesis in 22 patients with early syphilis during massive arsenotherapy. In 19, at least one of the four laboratory tests indicated impairment of hepatic function, prior to treat-

90. Thomas, L. J., and Olansky, S.: A Study of Liver Function Following Massive Arsenotherapy for Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:272 (May) 1946.

91. Kalz, F., and Steeves, L. C.: Decrease of Prothrombin Concentration in Massive Arsenotherapy, *Am. J. Syph., Gonorr. & Ven. Dis.* **28**:89 (Jan.) 1944.

92. Hoffman, M. M., and Kalz, F.: Studies on Liver Function: I. Liver Function in Early Syphilis Before and During Massive Arsenotherapy, *Am. J. Syph., Gonorr. & Ven. Dis.* **29**:596 (Nov.) 1945.

ment, although clinical evidences of hepatitis were absent. During arsenotherapy pronounced reduction of the blood prothrombin concentration occurred in 21 patients. In 10 patients, at least one of the other tests indicated impairment of hepatic function. Although the sensitive tests of hepatic function used in this study indicate that hepatic damage follows massive doses of arsenical drugs, in no instance was the damage sufficient to result in clinically recognizable signs and symptoms of hepatic disease. In patients who had a moderate degree of hepatic impairment before treatment there did not develop a severer grade of hepatic damage after therapy than there did in those whose hepatic function was normal. Function which was impaired during arsenotherapy was found to become normal within six months.

(To Be Concluded)

News and Comment

GENERAL NEWS

The Scientific Exhibit, Atlantic City Session of the American Medical Association.—At the Atlantic City Session, June 9 to 13, 1947, the American Medical Association will observe its centennial anniversary. For almost half of those hundred years—since 1899—the Scientific Exhibit has been a feature of each annual session and has developed into a short course in graduate medical instruction.

Exhibits at the 1947 Session will cover all phases of medicine. A certain amount of historical material will be included, but emphasis will be placed on the latest developments of medical science. The representative to the Scientific Exhibit from the Section on Internal Medicine is Dr. Thomas C. Garrett, 3803 Oak Road, Philadelphia.

Applications for space should be submitted as early as possible, since the closing date is Jan. 13, 1947. Application blanks may be obtained either from Dr. Garrett or from the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago 10.

Dr. Kendall Emerson to Attend Executive Committee Meeting of International Union Against Tuberculosis.—Dr. Kendall Emerson, managing director of the National Tuberculosis Association, will represent the voluntary tuberculosis associations of the United States when the Executive Committee of the International Union Against Tuberculosis meets in Paris November 7 to plan reorganization of the Union, activities of which were suspended during the war. He will be accompanied by Frederick D. Hopkins, executive secretary of the National Tuberculosis Association.

Measures for renewal and expansion of international relationships in the field of tuberculosis control will be discussed by the committee, which includes representatives of Great Britain, France, Poland, Belgium, Norway, Portugal, Italy and the United States. Also on the agenda is the question of cooperation with the World Health Organization of the United Nations. Proposals for financial support from member associations will be considered.

In discussing plans for American participation in the international organization, Dr. Emerson pointed out that tuberculosis has reached epidemic proportions in many parts of the world as a direct result of the war.

The Union was established in October 1920 as a "federation among the national associations and organizations engaged in the campaign against tuberculosis in the various countries of the civilized world." In countries in which there was no association, the appropriate government organization was the member agency. The purpose was to organize conferences, make studies, collect statistical information, stimulate scientific and social investigation and collect and distribute information to the members.

At the last conference of the Union in Lisbon in 1937, forty-three governments and national associations were listed as members. A conference scheduled to be held in Berlin in September 1939 was canceled by the outbreak of the war. Dr.

Emerson attended the last meeting of the Executive Committee in Paris in January 1939.

Dr. Emerson and Mr. Hopkins will attend by invitation a meeting of the Council of the National (British) Association for the Prevention of Tuberculosis in London before going to Paris.

Dr. Howard A. Rusk to Head New Department of Rehabilitation at New York University College of Medicine.—Dr. Howard A. Rusk, wartime Chief of the Army Air Forces Convalescent Services Program, has been named to head a new Department of Rehabilitation and Physical Medicine at the New York University College of Medicine.

The department will be the first of its kind in any medical college in the world, and will train all students through their medical college years in what is termed the "third phase of medical care"—preparing the patient to go from the bed to the job.

The department is an outgrowth and expansion of a division of physical medicine set up early last year as a part of the Department of Medicine under a grant of \$250,000 from the Baruch Committee on Physical Medicine in 1944.

Dr. George G. Deaver, clinical professor of physical medicine, is to continue as head of the physical medicine division of the new department.

The department will cooperate closely with the City Department of Hospitals in establishing and supervising rehabilitation programs in all city hospitals. Forerunner of the programs planned for other hospitals is that of Bellevue, at which severely disabled persons have been given rehabilitation treatment and training under the direction of Dr. Deaver for the past two years. A special rehabilitation program has recently been inaugurated at Sea View Hospital on Staten Island, and plans are under way to start other special rehabilitation projects at Goldwater Memorial Hospital.

Dr. Rusk was awarded the Distinguished Service Medal in 1945, was cited by the American Academy of Physical Education and received the American Design Award for his work in rehabilitation.

He is a member of the President's Committee to study governmental medical care, the Baruch Committee on Physical Medicine, the Medical Advisory Board of the American Legion and the Executive Council of the National Council on Rehabilitation.

Brazilian Society of Cardiology.—The third annual meeting of the Brazilian Society of Cardiology was held in the city of Belo-Horizonte July 24 to 30. The official subject of discussion was "Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Chagas Disease."

The next meeting will take place during the first fortnight of July 1947, in Sao Salvador da Bahia. The official subject proposed is "Hypertensive and Rheumatic Heart Diseases."

The newly elected officers for 1946-1947 are as follows: President: Prof. Edgard Magalhaes Gomes; Vice President: Prof. Octavio Magalhaes; General Secretary: Prof. Roberto Menazes de Oliveira; Second Secretary: Prof. Rinaldo Chiaverini; Treasurer: Dr. Luiz Murgel, and Director of Archives of Cardiology: Dr. Jairo Ramos.

All correspondence should be addressed to the Society as follows: Sociedade Brasileira de Cardiologie, Av. Mem de Sa 197, Rio de Janeiro, D. F., Brazil.

Book Reviews

Synopsis of Physiology. By Rolland J. Main, Ph.D. Price \$3.50. Pp. 341, illustrated. St. Louis: C. V. Mosby Company, 1946.

For the last ten years in the ARCHIVES OF INTERNAL MEDICINE there have been reviewed, from time to time, the synopses of different medical topics which have been published by C. V. Mosby Company. The ones seen have covered many subjects: heart disease, digestive disease, materia medica, pathologic chemistry, pathology, cutaneous disease, anorectal disease, syphilis and neuropsychiatry, to mention certain of them. Some have been as long as 671 pages and others as short as 302; the price has ranged, according to the size of the volume, from \$3.50 to \$6. On the whole, I have liked the series, my chief criticism being that the longer books were not really complete textbooks while the shorter ones attempted to compress too much subject matter into too little space.

Readers, on the other hand, appear to have appreciated the series thoroughly and particularly certain articles in it: Dr. George Herrmann's "Synopsis of Diseases of the Heart and Arteries" has been printed in three editions, for example, as has Dr. H. S. Crossen's "Synopsis of Gynecology," and the second edition of Dr. W. A. D. Anderson's "Synopsis of Pathology" has appeared recently. On the whole, therefore, C. V. Mosby Company is to be congratulated on having made popular a useful educational effort.

"Synopsis of Physiology" bids fair to assume a dignified position beside its sister publications. Physiology is discussed almost entirely as related to human beings, and the book admittedly is prepared for review purposes. It is the kind of text that a man returning to civilian life from the military will be glad to have within reach. The essentials of the subject are covered even though briefly and dogmatically, and there is a great deal of common sense, clinical medicine included, which many readers will find appetizing. The book can be recommended safely.

Annual Review of Physiology. By James Murray Luck, Editor, with an Editorial Committee. Volume 8. Price, \$5. Pp. 658. California: American Physiological Society and Annual Reviews, Inc., Stanford University, California, 1946.

Twenty-five reviews written by twenty-nine authors and co-authors constitute the eighth volume of this important publication. It is 658 pages in length and contains 3,602 references. A complete author and subject index makes possible easy reference to the wealth of information contained in the work.

In addition to the subjects routinely treated, shock, aviation physiology and audition have been reviewed.

The volume, as in previous editions, is well bound and excellently printed on paper of good quality.

Those who wish to keep abreast of the progress of research in pure and applied biology will find this work indispensable.

TYPHOID

Clinical Analysis of Three Hundred and Sixty Cases

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AND

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ALTHOUGH typhoid has received great attention throughout the medical literature of the past two centuries, we have been impressed by the scarcity of statistical reviews concerning this disease during the past several years and more particularly since the advent of sulfonamide therapy. It is therefore the purpose of this paper to review the cases of typhoid seen at Charity Hospital, New Orleans, during the six year period from Jan. 1, 1939 through Dec. 31, 1944, and to emphasize the clinical expressions of typhoid bacillus infections as seen during this period. Because of the magnitude of the task and the limitations of space, no exhaustive review of the literature will be attempted. Our series of 360 cases should, however, include examples of the difficulties most often encountered by physicians called on to diagnose typhoid and treat the patients.

CLINICAL FEATURES

During the six year period chosen for this study, 1939 through 1944, there were 360 cases of typhoid that we find acceptable for this series, according to the following criteria: (1) a positive blood culture; (2) a significant or rising agglutinin titer; (3) a urine or stool specimen containing typhoid bacilli; (4) a postmortem examination with findings considered pathognomonic of typhoid.

Incidence.—That the yearly incidence of typhoid in the United States is showing a downward trend is demonstrated in table 1. Five times as many cases were reported in 1930 as in 1944. It may also be seen that six Mississippi Valley states, Missouri, Kentucky, Tennessee, Arkansas, Mississippi and Louisiana, while showing a declining incidence, are still reporting far more than their expected number of cases as calculated from either the number of states or

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the percentage of the population represented. This may be due in part, however, to geographic and climatic factors. As may be seen from the last column, the downward trend of the number of cases of typhoid at Charity Hospital is in keeping with the trend for the nation and the Mississippi Valley area.

TABLE 1.—*Incidence of Cases of Typhoid and Paratyphoid in the United States as Compared with That of Cases in Certain Mississippi Valley States* During the Past Fifteen Years and That of Cases at Charity Hospital During the Past Six Years*

Year	Number of Cases in U. S. A.	Cases in Mississippi Valley		Number of Cases at Charity Hospital
		Number	Percentage of Total Number of Cases in U. S. A.	
1930.....	27,201	6,527	23.99	
1931.....	26,459	6,859	25.92	
1932.....	26,618	7,069	26.56	
1933.....	23,349	5,333	23.99	
1934.....	22,217	5,329	23.94	
1935.....	18,355	4,221	23.02	
1936.....	15,898	3,737	23.51	
1937.....	16,033	3,931	24.51	
1938.....	14,903	3,270	21.94	
1939.....	13,069	3,097	23.69	129
1940.....	9,809	2,370	24.17	76
1941.....	8,601	2,023	22.36	55
1942.....	6,678	1,555	23.29	43
1943.....	5,540	1,212	21.88	33
1944.....	5,388	1,053	19.27	24

* Included are Missouri, Kentucky, Tennessee, Arkansas, Mississippi and Louisiana.

The incidence of typhoid, in contradistinction to what one would expect, was well distributed throughout the four seasons (table 2), although it reached its peak during January and February. The only factor which we can suggest as explanatory of this seasonal distribution is the influence of climate.

TABLE 2.—*Seasonal Incidence of Three Hundred and Sixty Cases of Typhoid at Charity Hospital*

Month	Number of Cases	Percentage of Total Number of Cases	Month	Number of Cases	Percentage of Total Number of Cases
January.....	40	11.11	July.....	33	9.17
February.....	45	12.50	August.....	33	9.17
March.....	32	8.89	September.....	30	8.33
April.....	16	4.44	October.....	27	7.50
May.....	22	6.11	November.....	35	9.72
June.....	27	7.50	December.....	20	5.56

Racial Distribution.—Of the 360 patients, 221 were white and 139 were Negroes. Inasmuch as this is roughly proportional to the numbers of white and Negro patients admitted during the same period, no significant difference in racial susceptibility to the disease is indicated.

Sex.—There were 90 white females, 72 Negro females, 131 white males and 67 Negro males. These data reveal that 55 per cent of our patients were males. This is readily understandable, however, when one considers that males, because of occupational and other factors, usually have greater opportunity of taking the causative organism into their bodies.

Age.—The age factor is also related in a general way to the opportunities for contact of the patient group. The disease is considered to be relatively rare in the very young and in the aged. In our group 2 patients were less than 1 year of age; one was a white male infant of 8 months, while the other was a Negro female infant of the age of 9 months. Both these infants were said to have been breast fed, and there was no known occurrence of typhoid in either family. The oldest patient in this series was a white man of 71 years. The average age

TABLE 3.—*Age Incidence and Mortality Rate in Three Hundred and Sixty Cases of Typhoid in Five Year Periods*

Age	Number of Cases	Percentage of Total Number of Cases	Number of Deaths	Percentage of Mortality Rate
0 to 5.....	24	6.67	1	4.17
6 to 10.....	48	13.33	3	6.25
11 to 15.....	63	17.50	3	4.76
16 to 20.....	63	18.89	6	8.82
21 to 25.....	49	13.61	10	20.41
26 to 30.....	43	11.94	9	20.93
31 to 35.....	24	6.67	4	16.67
36 to 40.....	16	4.44	3	18.75
41 to 45.....	6	1.67	1	16.67
46 to 50.....	6	1.67	2	33.33
51 to 55.....	5	1.38	1	20.00
56 to 60.....	2	0.56	1	50.00
61 to 65.....	4	1.11	1	25.00
66 to 70.....	1	0.28	1	100.00
71 to 75.....	1	0.28	0	0.00

for our group of patients was 29.4 years. Table 3 shows the incidence of cases in five year periods.

Distribution in the Community.—Of the 360 patients, 84 (23.33 per cent) lived in New Orleans. Inadequate data failed to reveal how many of these patients had recently been in rural communities. One hundred and twenty-nine lived on farms, while 90 lived in rural communities and were engaged in farm work, fishing, hunting or trapping.

Occupational Factors.—Slightly more than a third of the entire group were children. Of the 360 patients, 219 lived on farms or in rural communities, and most of these were farmers, farmers' wives or children. Those whose occupations were associated with rivers, lakes or swamps included 18 fishermen, 5 trappers and 3 swamp loggers. Two oyster openers also contracted the disease. Three nurses, 2 hospital attendants and 1 undertaker were included in this series. Other occupational groups represented in this group varied greatly.

Vaccination.—Data concerning immunizations were incomplete. It was determined, however, that 41 patients living in areas where typhoid was endemic were said to have received three doses of vaccine within sixty days of the time that their illness began. Of these, 27 were exposed to typhoid in their own homes.

Sources of Infection.—About two thirds of this group of patients came from rural communities. Many had inadequate screening and toilet facilities, while about one fourth of these lived on the river or along the bayous. Many of these gave a history of drinking water of a well or a stream. Forty-nine of the group had been exposed to typhoid among members of their family, while 26 others knew of cases in their community. Of the 3 nurses in the group, 2 had nursed typhoid patients, while the 2 hospital attendants and 1 undertaker had also been in contact with human sources of infection. Over half the group previously mentioned as fishermen, trappers and swamp loggers had at one time or another drunk water that was potentially infected. About 20 per cent of the 360 patients, nearly all of these from New Orleans, said that they did not know of any possible sources of infection.

Period of Incubation.—Data obtained from this study do not permit an accurate determination of the period of incubation. Most of the patients giving a history of exposure had multiple opportunities to contract the disease. The period of incubation is said to range from three to twenty-one days, with the mean incidence between the eighth and fourteenth days.¹ The fewer the organisms that have entered the intestinal tract of the infected person the more prolonged is the period of incubation; the larger the number of organisms in the causal dose, the shorter is the period of incubation.

Onset.—Historical data obtained from the patients regarding the onset of their illness were in many instances none too reliable. Thirty-nine of the 360 patients (10.8 per cent) were said to have experienced a sudden onset of the disease, usually beginning as a transient chill. Of the remaining 321 patients, apparently adequate historical information was obtained from 296. As shown in table 4, malaise, headache and anorexia were the predominant prodromal symptoms. Respiratory symptoms occurred in nearly half the patients. Many patients also complained of one or more of the other symptoms in addition to the predominating triad of complaints. Of those patients who did not date the onset of their disease from a chill, the duration of prodromal symptoms before they were known to have fever or were confined to

1. Musser, J. H.: Typhoid Fever, in Piersol, G. M., and Bortz, E. L.: *Cyclopedia of Medicine, Surgery and Specialties*, Philadelphia, F. A. Davis Company, 1940, vol. 15, p. 501.

bed varied from two to eighteen days, with an average duration of about eight days for the group. Undoubtedly many of these patients had an elevation of temperature before they were aware of it.

Cutaneous Manifestations.—Although a few patients complained of severe sweats, the skin was usually dry. The two commonest conditions of the skin among our group of patients with typhoid were

TABLE 4.—*Incidence of Prodromal Symptoms in Two Hundred and Ninety-Six Cases of Typhoid*

Prodromal Symptom	Number of Cases	Percentage
Malaise.....	208	90.54
Headache.....	249	84.12
Anorexia.....	236	79.73
Cough.....	119	40.20
Sore throat.....	117	39.53
Thirst or dry mouth.....	110	37.16
Restlessness.....	83	28.04
Early abdominal pains.....	63	21.28
Early diarrhea.....	30	10.14
Epistaxis.....	13	4.39

rose spots and bedsores. Table 5 indicates the incidence of rose spots in the two racial groups. Nearly every Negro patient presenting these lesions had light-colored skin. The rose spots seen on the white patients usually consisted of slightly elevated, rounded, pale pink spots, from 2 to 4 mm. in diameter. These spots, which blanched on pressure, characteristically appeared on the ninth day of the disease but were first observed in some instances as early as the fourth or as late as

TABLE 5.—*Incidence of Rose Spots Among White and Negro Patients with Typhoid*

Race	Number with Rose Spots	Number with No Rose Spots	Percentage with Rose Spots
White.....	92	111	45.32
Negro.....	19	112	14.50
Total.....	111	223	33.23

the twenty-first day of illness. The abdomen, the chest, the back, the extremities and the face were involved in that order of frequency. The face, however, was involved but 6 times (5.4 per cent), while lesions of the palms, the soles and the scalp were not observed. About one third (36) of these 111 patients had two or more crops of rose spots, each crop varying from four or five to forty or more spots. Individual crops of rose spots, which did not itch, usually lasted from two to five days and disappeared without leaving any trace. No hemorrhagic manifestations were noted.

Bedsore, usually over the sacrum, were present in 46 patients (12.78 per cent) and were merely indications of pressure and uncleanness rather than pathognomonic lesions of typhoid. Multiple furunculosis was seen in 8 patients. Typhoid bacilli were isolated from furuncles of 3 of these patients. Herpes labialis was observed but 7 times (1.94 per cent), pneumonia being a complicating factor in 3 of these instances, and was most conspicuous by its absence.

Temperature.—Thirty-nine of our patients suffered a transient chill at the onset, while 69 others experienced a chill within the first few days of illness. Of the 108 patients that experienced chills at some time during the course of their illness, 72 (66.7 per cent) suffered multiple transient chills, sometimes two or three within twenty-four hours. The average number of days during which chills occurred in this group was 3.2. After the actual onset, which was frequently difficult to determine, the temperature characteristically began to rise by successive steps, usually reaching its maximum by the tenth day. There were apparently, however, a few instances in which the temperature rose suddenly and reached its peak within forty-eight hours, while in a few others the temperature curve was without any tendency toward regular progressive elevation. The maximum temperature, according to recordings in our series, varied from 102 to 108.8 F. and averaged about 104.2 F.

After the temperature reached its maximum by the so-called step-ladder ascent, it was found to maintain its height for approximately eleven days. During the ascent the daily variations were usually not more than 1 or 1.5 F. After the maximum was reached, however, the daily fluctuations averaged 2.2 F. while ranging from 1 to 4 F. Some of the wide variations were probably due to vigorous use of temperature-reducing measures.

After the period of continued fever, the high temperature began to have more pronounced remissions, usually in the mornings. Once defervescence had begun, the temperature, which always fell by lysis, required from three to eighteen days to reach normal, and the average number of days required for lysis to occur was 7.8. Forty-five patients without true chills complained of chilly sensations, nearly all of these occurring during the period of defervescence, when the daily variations in temperature were greater than at any other time during the disease. Thus it was found that the average duration of fever for the entire series exclusive of the cases in which death occurred was 31.5 days. The duration of fever varied from seventeen days in a few cases to one hundred and nine days in another.

Relapses were observed in 45 cases. The average time required for fever to reappear was nine days, but it varied from three to thirty-eight days. The duration of these relapses, ranging from five to thirty-nine

days, was 15.6 days. Second relapses, which did not vary essentially from the initial ones, were observed five times.

Neuromuscular Manifestations.—Nervous manifestations were common in our patients. Table 6 shows the incidence of various neuromuscular manifestations that occurred at some time during the disease of the group. Headache, insomnia and dizziness were relatively early symptoms, while headache, apathy, delirium, stupor and, at times, coma were observed later in the disease, and their severity was usually dependent on the severity of the toxemia associated with the disease. Pain in the neck, nuchal rigidity or other neurologic manifestations caused lumbar punctures to be done on 46 of these patients (12.78 per cent). One patient, a Negro youth of 17, was found to have an elevated level of protein in the spinal fluid and over 900 cells per cubic millimeter; culture of the spinal fluid yielded *Eberthella typhi*. He

TABLE 6.—*Incidence of Neuromuscular Manifestations in Three Hundred and Sixty Cases of Typhoid*

Manifestations	Number of Cases	Percentage
Generalized muscular aches and pains.....	328	91.11
Headache.....	325	90.28
Weakness and apathy.....	312	86.67
Pain in back.....	273	75.83
Stupor.....	261	72.78
Delirium.....	150	41.67
Insomnia.....	93	25.83
Dizziness.....	90	25.00
Coma.....	55	15.28
Pain in neck.....	49	13.61
Stiff neck.....	35	9.72
Psychosis.....	7	1.94

eventually recovered. Delirium was usually manifested by a low muttering, but mania, sometimes accompanied with delusions and periods of melancholia, was also seen. Seven of the group exhibited psychosis after all other evidence of disease had disappeared—an incidence of psychosis of 1.94 per cent. With some of them it was a month or more before sufficient improvement had taken place to warrant discharge from the hospital.

Other outstanding symptoms noticed during the course of the disease included generalized muscular aches and pains, pain in the back which in a few instances led to an admission diagnosis of pyelonephritis, and weakness. Weakness, the last to disappear, usually became less evident as convalescence progressed. Flexion contracture of the right hip, which responded to traction and physical therapy, was seen as a sequel in 1 patient, while transient paralysis of the lower extremities requiring physical therapy was observed in another.

Special Senses.—Severe aching or soreness of the optic muscles was not a complaint of the patients. Photophobia was noticed in less

than 5 per cent of the 360 patients. Conjunctival injection, in contradistinction to observations among a large series of patients suffering with endemic typhus fever,² was observed in but 3, while purulent conjunctivitis occurred in 1 patient. Transient partial deafness was a complaint of 5 patients, while tinnitus was a complaint of 19 (5.28 per cent). Otitis media developed in 5 instances (1.39 per cent), while mastoiditis necessitating surgical intervention was observed in 2 of these.

Respiratory Manifestations.—Some evidences of involvement of the respiratory tract were present in most of the patients. Coryza, sore throat and manifestations of bronchitis were commonest (table 7). Cough, present in 310 patients, was usually nonproductive, but mucopurulent sputum was raised by several and blood-tinged sputum was produced a few times, usually in patients with clinical and roentgenologic evidences of bronchopneumonia. Nosebleed, at times rather severe,

TABLE 7.—*Incidence of Respiratory Manifestations in Three Hundred and Sixty Cases of Typhoid*

Manifestations	Number of Cases	Percentage
Coryza.....	315	87.50
Cough.....	310	86.11
Sore throat.....	304	84.44
Rales.....	231	64.17
Pain in chest.....	216	60.00
Cyanosis.....	129	35.83
Epistaxis.....	75	20.83
Pneumonia.....	41	11.39
Pleurisy.....	6	1.67
Pleural effusion.....	2	0.56

was present at some stage of the disease, usually early, in 75 patients. Pain in the chest, a complaint of 60 per cent of the group, was frequently nothing more than a soreness and possibly due to the cough associated with bronchitis. Rales, showing great variation in character and number, were heard in about 65 per cent of the patients. Although associated with pneumonitis in some instances, they were more commonly an indication of some degree of hypostatic pulmonary congestion and were heard oftenest during the more severe stages of the disease. Pneumonia, most often thought to be due to secondary bacterial invaders, was present forty-one times, an incidence of 11.39 per cent. Pneumococci were isolated from the sputums of 3 patients. One patient presenting clinical and roentgenologic evidences of pneumonia was found from cultures of the sputum to have typhoid bacilli in the sputum. There were no ulcers in this patient's pharynx or larynx that could be demonstrated. Respiratory rates were increased, the maximum respira-

2. Stuart, B. M., and Pullen, R. L.: Endemic (Murine) Typhus Fever: Clinical Observations of One Hundred and Eighty Cases, *Ann. Int. Med.* 23:520, 1945.

tions recorded averaging about 32 per minute in uncomplicated cases, and steadily increased (to 50 or more in 18 patients) when bronchopneumonia or severe intestinal hemorrhage developed. The incidence of other manifestations of involvement of the respiratory tract is indicated in table 7.

The symptoms and signs of involvement of the respiratory tract were present in severe enough forms to cause 154 of the patients (42.78 per cent) to be subjected to roentgenologic examination of the chest, several having two or more such examinations. In 98 of these 154 patients the roentgenograms were considered to show an entirely normal respiratory tract; in 1 the roentgenogram showed evidences of pulmonary tuberculosis, thought to be inactive. In 37 of the remaining patients the roentgenograms revealed bronchopneumonia, while the roentgenograms of the other 18 were interpreted as showing signs of peribronchial thickening or hilar enlargement.

Cardiovascular Manifestations.—Symptoms referable to the cardiovascular system were varied. During the first week of disease, before the temperature had reached its maximum, the pulse was most often slow in relation to the height of the temperature. The average maximum pulse rate during this period was, however, for those patients entering the hospital during their first week of illness, 96 beats per minute. A dicrotic pulse was detected in 119 patients (an incidence of 33.06 per cent), and characteristically it appeared after the temperature had completed its ladder-like ascent and while the toxic manifestations of the disease were evident. Dicrotism was first detected on the average on the thirteenth or the fourteenth day of illness and usually disappeared whenever the heart action became rapid but was first observed as early as the seventh and as late as the twenty-third day. One patient, a white man of the age of 42, survived his initial bout of fever lasting twenty-seven days without evidence of a dicrotic pulse being detected. During a remission, however, which occurred after seven afebrile days, he had a dicrotic pulse on the eleventh day of the relapse, and he died on the twenty-ninth day of the relapse, with evidences of bronchopneumonia in addition to heart failure associated with hypertensive heart disease. During the second and third weeks of the disease, when toxemia was usually most evident, our patients with typhoid usually showed an increase of pulse rate which was in many instances proportional to the degree of fever present at the time. If we exclude all cases with complications considered capable of causing an increase of pulse rate, which includes all the cases in which death occurred, the maximum pulse rate recorded at some time during the disease averaged 122 per minute but varied from 100 to 144 per minute. The average maximum pulse rate for the 360 patients was 130 per minute.

Blood pressure readings recorded early in the disease were usually within normal limits. In those patients whose blood pressures were recorded regularly, however, there was a gradual and consistent fall during the febrile course. Drops as great as 40 mm. systolic and 30 mm. diastolic, without evidence of contributory complicating factors, were observed in a few instances; however, the usual change was only about one half as great. Severe drops in blood pressure were detected in several patients experiencing large intestinal hemorrhages. Transitory elevations in blood pressure, about 15 mm. of mercury in each instance, were observed in 2 patients in whom intestinal perforations were developing; the elevation was observed to persist for two hours in one instance, and was known to be present for five hours in the other.

The heart sounds and rhythm were usually normal at the onset of the disease in our series of patients with typhoid. During the more severe stages of the disease, however, a systolic murmur, usually soft and blowing in character, was heard in 112 patients (31.11 per cent). This murmur was heard oftenest in the mitral or the pulmonic area and was heard in both valvular areas in a few cases. Most of these patients had no evidence of heart murmurs when discharged from the hospital. In 32 patients (8.89 per cent) a rapid heart rate developed during the course of their illness, resulting in auscultatory findings which resembled embryocardia.

Clinical evidence of cardiac decompensation due to preexisting disease was seen in 10 patients. Five of these had hypertensive heart disease; 4 had evidences of arteriosclerotic heart disease, 1 with auricular fibrillation, and the remaining 1 was a Negro man of 29 who had syphilitic heart disease. Among the 6 of the 10 that died were 4 with hypertensive heart disease, 1 with arteriosclerotic heart disease and the Negro patient with syphilitic heart disease. Heart failure was apparently responsible for 3 of the deaths, while complications, such as intestinal hemorrhage or bronchopneumonia, were at least contributory causes of the other 3 fatalities.

Electrocardiographic studies were made on 16 patients, excluding those with preexisting heart disease, suspected to have myocarditis or some other cardiac complication. Of these 8 had only sinus tachycardia; 1 had slight right axis deviation; 1 had an abnormally long P-R interval (patient, 18 years of age, had a heart rate of 110 beats per minute when tracings were made); 1 had changes (slight elevation of S-T segments in leads I, II and III compatible with pericarditis), and 5 presented changes more consistent with toxic myocarditis. These changes included low T waves in all leads, inverted T₄ and notchings of R₂ at the base of the upstroke. Most of these patients had evidences of cardiac weakness during the more advanced stages of the disease, but all recovered. There was, however, 1 patient not subjected to electrocardiographic

studies, a white man of 28 years, whose postmortem examination revealed toxic myocarditis and pulmonic and hepatic congestion in addition to typhoid ulcerations of the ileum. There were therefore 6 patients with evident myocarditis, an incidence of 1.67 per cent, among this group.

One example of endocarditis was found at autopsy. A 67 year old white man had the onset of his illness twenty-five days before his admission to the hospital and had shown considerable improvement in his condition until three or four days before his admission. Recurrent fever and malaise were complaints on admission, and two blood cultures were positive for *E. typhi* before death occurred on the sixth day of hospitalization.

Venous thrombosis was recognized but three times (0.83 per cent) among our 360 patients with typhoid. This incidence is considerably less than that generally reported in the literature.³ Evidences of venous thrombi, involving the left femoral vein in 2 instances and the right

TABLE 8.—*Incidence of Certain Gastrointestinal Manifestations Seen in Three Hundred and Sixty Cases of Typhoid*

Manifestations	Number of Cases	Percentage
Anorexia.....	327	90.88
Abdominal tenderness.....	303	84.17
Constipation.....	283	78.61
Abdominal distention.....	275	76.39
Foul breath and sordes.....	249	69.17
Nausea and vomiting.....	196	54.44
Diarrhea.....	156	43.33
Gross intestinal hemorrhage.....	76	21.11
Intestinal perforation.....	7	1.94
Herpes labialis.....	7	1.94
Parotitis.....	2	0.56
Ulceration of upper part of gastrointestinal tract.....	1	0.28

popliteal vein in the third, were noticed during the third week of the patient's disease in each instance. Each patient recovered without any indications of pulmonary embolism taking place. One patient with occlusion of the left femoral artery was observed, but eventual recovery without sequelae was seen to occur.

Gastrointestinal Manifestations.—Although typhoid is a disease which is essentially septicemic in nature, the outstanding gross pathologic changes are usually related to the small intestine. It is to be expected therefore that gastrointestinal manifestations of typhoid should be frequent and in many instances dangerous to life. The incidence of the gastrointestinal manifestations among our 360 patients with typhoid is shown in table 8.

3. Bercovitz, Z. T.: Typhoid Fever, in Bercovitz, Z. T.: Clinical Tropical Medicine, New York, Paul B. Hoeber, Inc., 1944, p. 548.

Anorexia, frequently a prodromal symptom (table 4), was present in over 90 per cent of the patients. Distaste for food, clinically significant from the standpoint of therapy, became more pronounced as the disease progressed, but it was usually replaced by an increasing desire for food as defervescence took place.

Diarrhea, a prodromal complaint of only about one tenth of the patients, was present at some time during the illness of 156 patients. The duration and the severity of the diarrhea, which most often had its onset by the eighth or the ninth day of illness, varied greatly. Diarrhea of a not inconsiderable severity, lasting but two or three up to fifteen days or more, was seen and in a few cases was thought to be an outstanding factor in the exhaustive state which preceded death. In some cases stools, frequently with a foul odor and characterized by a pea soup appearance, were passed twenty or more times a day. Severe, protracted diarrhea was, however observed in only 89 patients, an incidence of about 25 per cent. Several of the group passed stools two or three times a day, which were soft or semiformal in character, but these passages were not considered to be examples of true diarrhea.

Constipation, occurring either throughout the course or at some stage of the disease, was a complaint of 283 patients, an incidence of 78.61 per cent. Among those patients in whom diarrhea did not develop constipation was most troublesome during the second and third weeks but frequently persisted until convalescence was well established. About two thirds of the patients suffering from diarrhea, excluding the ones who died, experienced constipation after diarrhea had ceased. In general, it may be said that constipation, while twice as frequent as diarrhea, was of much less clinical significance from the standpoint of complications leading to death.

Abdominal tenderness was detected in 303 patients, but only 70 patients (19.44 per cent) complained of abdominal pain, which was usually not of a severe nature. Both tenderness and pain were usually observed after the first week of illness had passed; they were present in all abdominal quadrants but were most characteristically located in the right lower quadrant. The location of abdominal tenderness, in some instances associated with pain, in patients with typhoid, as determined from 303 patients of this series, is indicated in table 9.

Abdominal distention was present at some time during the period of illness in 275 patients (76.39 per cent) but was usually not severe unless associated with profound toxemia or diarrhea. Meteorism was, however, a potential danger because of the fact that intestinal hemorrhage or perforation occurred oftenest among the patients with gaseous distention. In 30 patients abdominal distention was so severe that Wangenstein's suction apparatus was utilized to supplement measures routinely employed to relieve this condition. Seventy-six patients, 21.11

per cent. of the 360 in this series, had at least one intestinal hemorrhage of sufficient volume to be detected macroscopically. The average duration of disease before hemorrhage was first detected was 15.7 days, but initial episodes of intestinal bleeding ranged from the seventh to forty-first day. In some cases the volume of blood lost was only moderate and seemed to have little influence on the progress of the disease, but a few patients suffered hemorrhages either so massive or frequent that the prognosis was materially changed. Although intestinal bleeding was not the responsible factor in many instances, 26 of the 76 patients (an incidence of 34.21 per cent) who suffered the loss of grossly visible blood from bleeding typhoid ulcers of the intestine eventually died. Intestinal hemorrhage occurred in all but 1 patient with intestinal perforation and was first detected before the perforation took place in all but 1 instance. From the available data it is indeed doubtful that periodic blood cell counts, especially erythrocyte counts, are of much value as an evidence

TABLE 9.—*Location of Abdominal Tenderness Among Three Hundred and Three Cases of Typhoid*

Location	Number of Cases	Percentage
Right lower quadrant of abdomen.....	158	52.15
Diffuse, generalized.....	69	22.77
Epigastric.....	25	8.25
Umbilicus.....	20	6.60
Left upper quadrant of abdomen.....	12	3.96
Right upper quadrant of abdomen.....	11	3.63
Left lower quadrant of abdomen.....	8	2.64

of intestinal bleeding. Both the anemia, which may be moderately severe during the period when intestinal hemorrhage is most prevalent (fig. 6), and the concentration of blood which frequently follows an appreciable loss of its fluid content make it apparent that hemorrhages of sufficient quantity to be reflected in the peripheral blood picture will usually be self evident. Although a daily determination of the urea nitrogen concentration in the blood may serve as a fairly reliable warning that intestinal bleeding has occurred,⁴ it is probable that regular examination of the feces of each patient to determine the presence of occult blood will oftener indicate the presence of small quantities of blood. Chemical evidence of blood was found in the stools, which were repeatedly examined, of 52 per cent of the patients in this series, excluding 76 patients in whom gross hemorrhage was apparent.

Of 11 patients presenting clinical evidence suggestive of intestinal perforation, 2 were not subjected to surgical abdominal exploration or to postmortem examination. Another patient who did not receive the benefit of a surgical abdominal exploration was found at autopsy to

4. Ingegno, A. P.: The Elevated Blood Urea of Acute Gastrointestinal Hemorrhage and Its Significance, *Am. J. M. Sc.* 190:770, 1935.

have a perforation of the ileum. Eight abdominal exploratory operations were performed and revealed 4 examples of perforation situated in the lower part of the ileum, 2 instances of perforation of the appendix and 2 instances in which pathologic changes were not found. There were, therefore, 7 proved instances of perforation, 5 of the ileum and 2 of the appendix, 2 others with a clinical picture strongly suggesting that perforation had occurred, and 2 in which surgical abdominal exploration failed to reveal the presence of intestinal perforation. The average duration of disease in those patients known to have a perforation was nineteen days, but this complication was seen as early as the twelfth and as late as the twenty-seventh day. Of the 8 patients who underwent surgical abdominal exploration, only 3 survived—1 with a perforation of the ileum, 1 with a perforation of the appendix and 1 of those patients whose examination did not disclose the presence of any perforation. In the other patient whose abdominal exploratory operation failed to reveal any perforation there developed, in addition to intestinal hemorrhage, diarrhea and meteorism of such severity that evisceration occurred at the site of the surgical incision on the eleventh postoperative day. Death occurred a few hours later. In summarizing, it may be said that of 7 patients known to have intestinal perforation, 5 with perforations of the ileum and 2 of the appendix, 5 died (a mortality rate of 71.43 per cent) and that only 3 of 8 patients subjected to surgical abdominal exploration left the hospital alive, indicating that the mortality associated with this procedure was 62.5 per cent.

Ulceration located in the upper portion of the gastrointestinal tract, which is thought to be an infrequent manifestation of typhoid,⁵ was observed in but 1 patient of this series. Ulcers thought to be examples of typhoid ulceration were observed, in addition to intestinal ulceration with generalized peritonitis due to perforation, to be present in both the esophagus and the stomach at the time of the postmortem examination, which was performed about two hours after death had taken place, on the twelfth day of the disease.

Of the other gastrointestinal manifestations listed in table 8, foul breath, sordes and nausea, generally accompanied with vomiting, require little comment. These conditions were usually most evident during the time when the disease was at the height of its severity. Herpes labialis was infrequently observed, and suppurative parotitis, in each instance requiring surgical incision and drainage, was observed but twice.

Liver and Gallbladder Manifestations.—Enlargement of the liver, sufficiently great to be clinically evident was present in 91 of these patients, an incidence of 25.28 per cent. Unquestionably an indication

5. Holmes, W. H.: *Bacillary and Rickettsial Infections*, New York, The Macmillan Company, 1940, p. 185.

of cardiac failure in a few patients, these examples of hepatomegaly were in most instances considered attributable to the typhoid infection. Enlargement of the liver was usually observed after the first week of illness and most often persisted throughout the period of a marked elevation of temperature, but it usually became less evident as defervescence progressed. Jaundice, confirmed by determinations of the icterus index, was clinically apparent in but 13 patients (3.61 per cent of the group) and was associated with involvement of the bile passages in only 6 cases in which subsequent surgical or postmortem examination was performed. In contradistinction, however, the cephalin flocculation test,⁶ which in each instance showed a strong (4 plus or 3 plus) reaction, indicated the presence of severe hepatitis in 3 of these 13 patients. Later cephalin flocculation tests done for 2 of these 3 patients after convalescence was well established were interpreted as negative.

There were in this series of 360 patients with typhoid but 10 who apparently had cholecystitis (an incidence of 2.78 per cent). Of the 10 patients, 3 had suffered no symptoms referable to involvement of the gallbladder, and there were only 4 known instances of associated cholelithiasis. Three patients subjected to necropsy had evidences of acute cholecystitis. In 4 of the other 7, during the course of their disease, clinical conditions suggesting cholecystitis developed, whereas 2 patients had apparently mild infections which did not suggest the presence of complicating factors. The last of the 7 patients, employed by a large dairy, was discovered, during a public health survey, to be a carrier of typhoid bacilli.

Each of the 7 patients whose illness did not terminate in death was found to have stools that contained typhoid bacilli after the disease had run its course. Specimens of bile obtained from each of these patients were cultured and yielded *E. typhi*. Four of the 7 patients were subjected to cholecystectomy. Although there was no death due to operation on the gallbladder, only 2 of the patients no longer passed typhoid bacilli in their stools after that procedure had been carried out.

It is surprising that the number of patients with clinically apparent cholecystitis (2.78 per cent of this group) and of carriers of typhoid bacilli (1.67 per cent in our series) is not greater than usually found. It is, from the bacteremic nature of the disease, inevitable that the gallbladder become infected in typhoid. Moreover, the typhoid bacillus, unlike many bacteria, such as the streptococcus and the pneumococcus, grows readily in a medium containing bile. An experiment by Gay⁷ has shown that typhoid bacilli injected into the vein of a rabbit can be

6. Gutman, A. B., and Hanger, F. M., Jr.: Differential Diagnosis of Jaundice, *M. Clin. North America* 25:837, 1941.

7. Gay, F. P.: Typhoid Fever Considered as a Problem of Scientific Medicine, New York, The Macmillan Company, 1918.

recovered within half an hour from the gallbladder. Certainly it would appear that the hematic dissemination of the typhoid bacilli in patients with typhoid is probably due in part to the passing of bacilli from the intestinal lesions to the liver by the portal vein. Therefore, every patient should have cultures made of the stools in an effort to determine whether typhoid bacilli are present after the disease has run its course. Three negative cultures are required prior to the patient's discharge in most localities.

Splenomegaly.—Physical examination of the 360 patients revealed enlargement of the spleen in 229 (63.61 per cent). This enlargement, noticed by the end of the first week of the disease in a not inconsiderable number of patients, usually rapidly disappeared as clinical improvement became apparent.

Genitourinary Manifestations.—Abnormalities referable to the genito-urinary tract were not prominent. Nevertheless, there were 7 patients (1.94 per cent) thought to have a complicating pyelonephritis, while in 9 patients there apparently developed cystitis, an incidence of 2.5 per cent. Retention of urine in the bladder was observed but once, and, likewise, only 1 instance of the urine being retained in the renal pelvis was detected. There were, however, 81 patients of our series (22.5 per cent) who had typhoid bacilluria at some time during the course of the disease. Although a few of the organisms persisted for a time after the disease had run its course, there were apparently no true examples in this group of persons becoming typhoid carriers because of bacilli in the urine.

Pregnancy and Typhoid.—Six women of this series were pregnant at the time of their admission to the hospital. Four of these pregnancies, ranging from two to six months in duration, resulted in abortions which ranged from sixteen to thirty-five days after the onset of the disease, while the average duration of disease before the uterus expelled its contents was twenty-four days. The other 2 women, who were pregnant at the time of admission, expected to deliver within the next three or four weeks. In both instances the disease apparently hastened the onset of labor, but both infants were born alive. One of the infants was kept in the hospital for several weeks after the mother's recovery. The apparent reason for this was that the child showed abdominal distention, diarrhea characterized by stools of a pea soup character and enlargement of the spleen. Unfortunately no diagnostic laboratory measures were utilized for this patient who was not included among our 360 patients, all of whom had significant laboratory data or postmortem examinations.

LABORATORY DATA

Although about two thirds of these patients entered the hospital with a presumptive diagnosis of typhoid, great variations in the severity

of symptoms referable to the various physiologic systems of the body were seen. Consequently, this group of patients was subjected to a large number of laboratory tests. Blood cultures, determinations of agglutinin titers and cultures of urine and stools all were obtained for nearly every patient and were for many patients repeated several times. Blood smears in a search for malaria were done thirty-nine times. For 58 patients one or more determinations of the blood urea concentration were made; for 21, determinations of the icterus index; for 39; determinations of the blood sugar, and determinations of serum protein, albumin-globulin ratio, carbon dioxide-combining power and blood chlo-

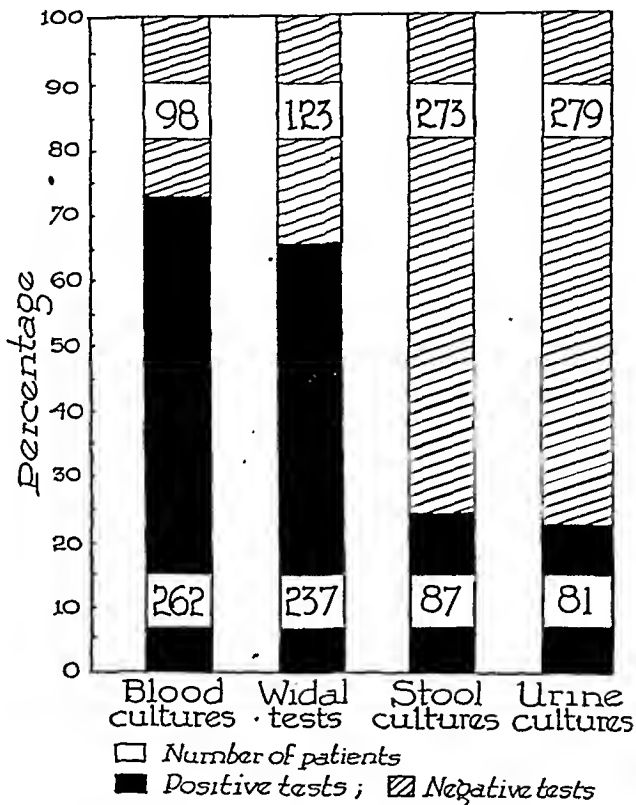


Chart 1.—The number and percentage of 360 patients with typhoid who had a positive blood culture, a positive Widal test, and stool and urine cultures showing the organism at some time during the disease.

ride and the cephalin flocculation test were each carried out in a few instances. The sputum of 28 patients was examined in a search for pneumococci, while 46 patients had surveys made of their spinal fluid. Other laboratory determinations, in addition to those discussed in the following paragraphs, were made infrequently.

Blood Culture.—A positive blood culture is the earliest and most conclusive laboratory evidence of typhoid that may be found. Of 360 patients, only 98 (fig. 1), most of those entering the hospital after the second week of illness, were not found to have typhoid bacteremia.

Blood culture should, however, not be delayed too long (fig. 2) because the incidence of positive blood cultures falls off rapidly as the disease progresses. The total number of blood specimens taken from our patients for culture was 832, and 336 of these (40.38 per cent) were positive (fig. 3).

Widal Agglutination Test.—Demonstrating the presence of agglutinins, so that when the serum from the blood of a patient with typhoid

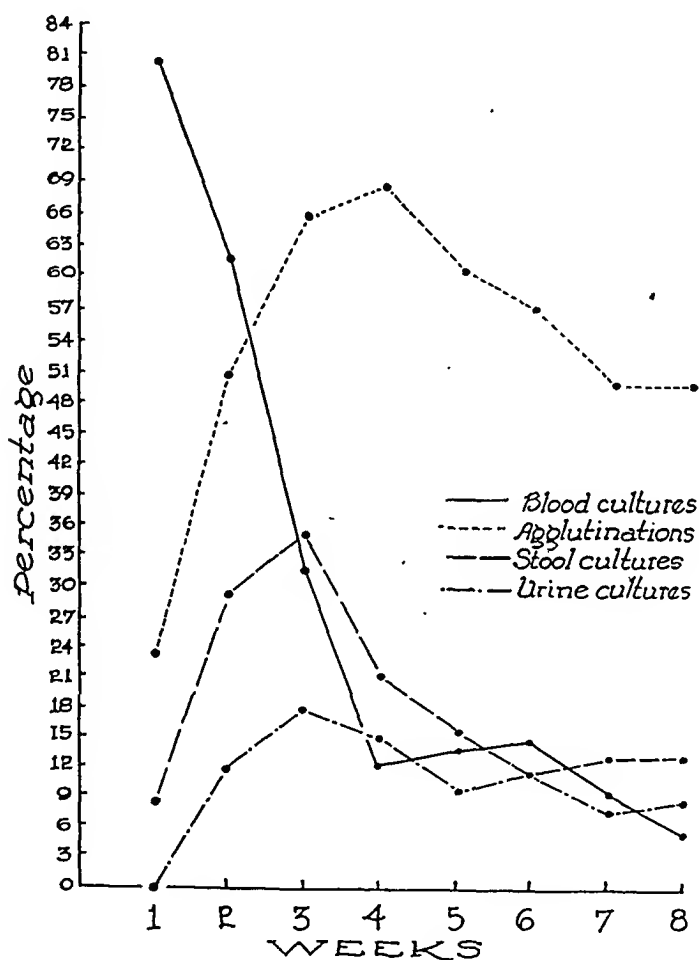


Chart 2.—A composite graph of the agglutinations and cultures for *E. typhi* of blood, stool and urine specimens from 360 patients taken at various intervals throughout a period of eight weeks.

is added to a culture of typhoid bacilli the agglutination test of Widal is obtained, is of great diagnostic value, but it has definite limitations. Thus it was found (fig. 1) that only 237 of our 360 patients (65.83 per cent) had agglutinins demonstrated in their blood serum at any time during the course of their disease. Whether or not this was due to the fact that the Widal reaction, frequently negative in the low titers usually employed to carry out the test, was not carried to a high titer

in these instances we were unable to determine. Figure 2 reveals the increasing incidence of positive Widal reactions as the disease progresses, but figure 3 shows that, of 933 Widal tests, only 546 (58.52 per cent) were positive in significant titers.

Cultures of Stools.—Only 87 of our patients had one or more positive cultures of stool (fig. 1), while only 318 of 1,442 cultures of stools (22.05 per cent) contained organisms (fig. 3). Typhoid bacilli were most often cultured from the stools of our patients during the third week of the disease (fig. 2).

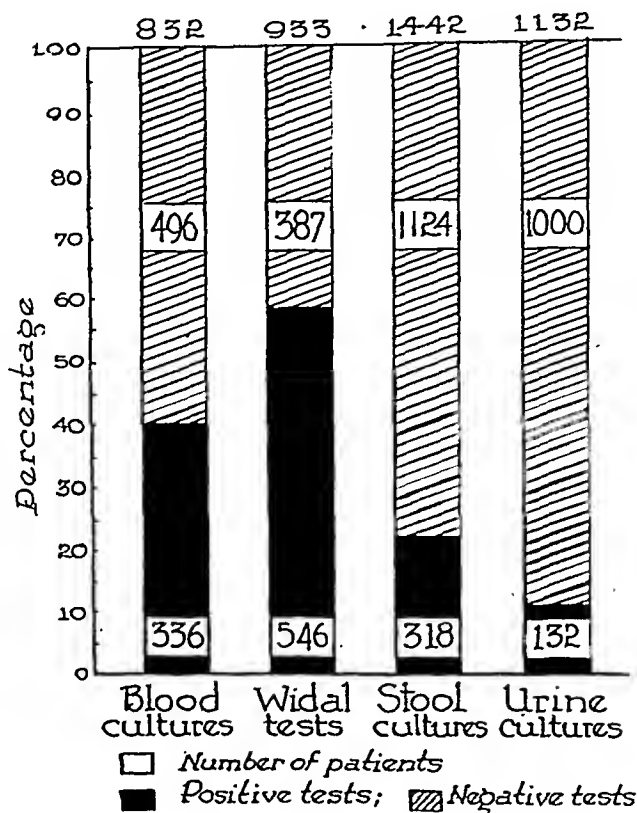


Chart 3.—The total number and the percentage of blood cultures, Widal tests and stool and urine cultures that were positive at some time throughout the illness of 360 patients.

Blood Picture.—While the cellular aspect of the blood is none too characteristic in many instances, it was found from an analysis of 721 white blood cell counts made for our patients (fig. 4) that there is usually a transient rise in the white blood cell count during the first ten days of the disease. Following this increase, a fairly rapid and progressive leukopenia, primarily due to a decrease in the number of polymorphonuclear cells, which results in a relative increase of the mononuclear cells of the peripheral blood (fig. 5), was found to reach its maximum severity at the end of the third week of the disease. Counts ranging from 1,200 to 20,000 cells were seen in apparently uncomplicated cases. Appreciable changes in the white cell count were usually lacking in

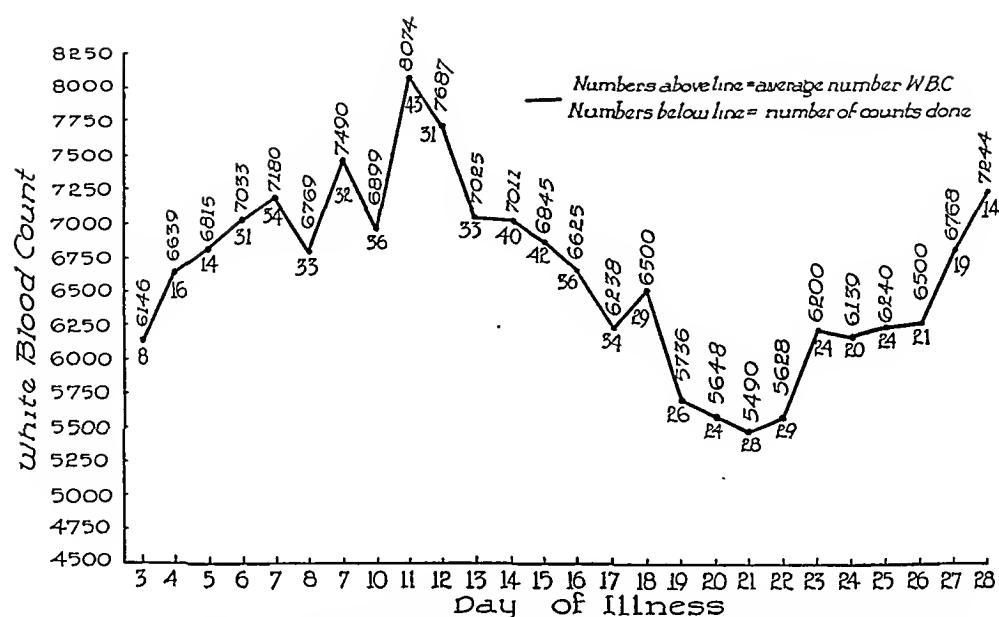


Chart 4.—Average white blood cell counts per day of illness of patients with uncomplicated typhoid, based on a total of 721 determinations.

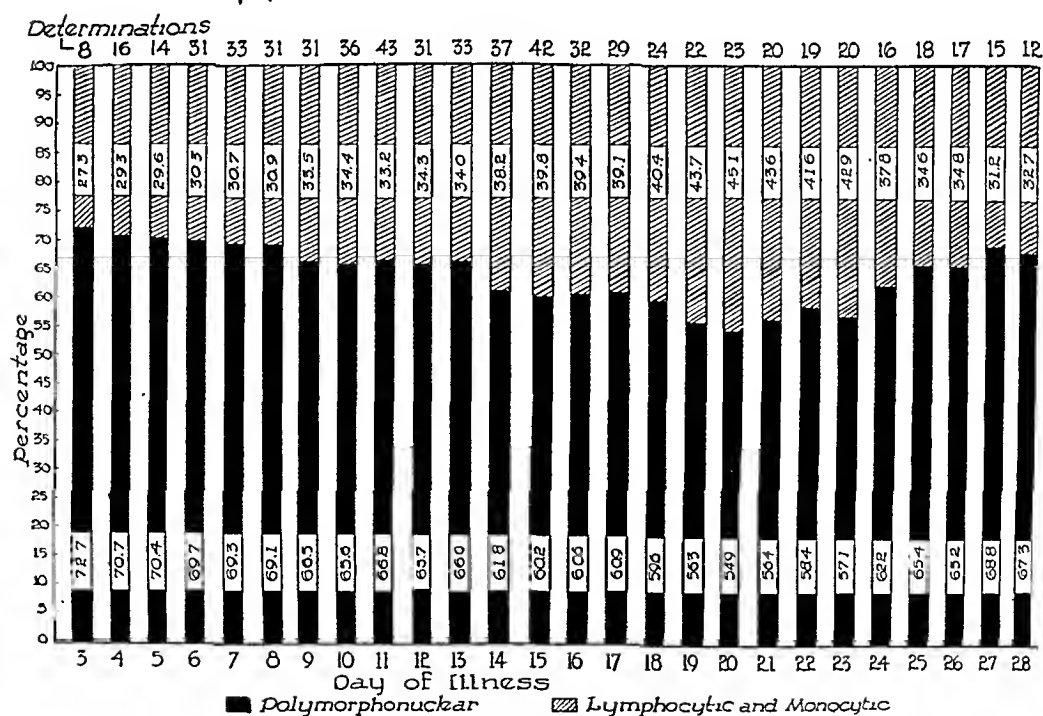


Chart 5.—Average ratio of polymorphonuclear to lymphocytic and monocytic cells per day of illness, based on 653 differential white cell studies. The total number of determinations is represented at the top of each column.

cases in which there was severe hemorrhage or intestinal perforation, complications which were most often seen during the period of relative leukopenia, which has been attributed to lesions of the red bone marrow.

Anemia was found to develop relatively rapidly among our 360 patients. Figure 6 shows the average red blood cell count per day, excluding those patients with gross evidences of intestinal hemorrhage. The maximum change in this count, too, was observed to occur at the end of three weeks and was followed by an increase in the erythrocyte count as convalescence was established.

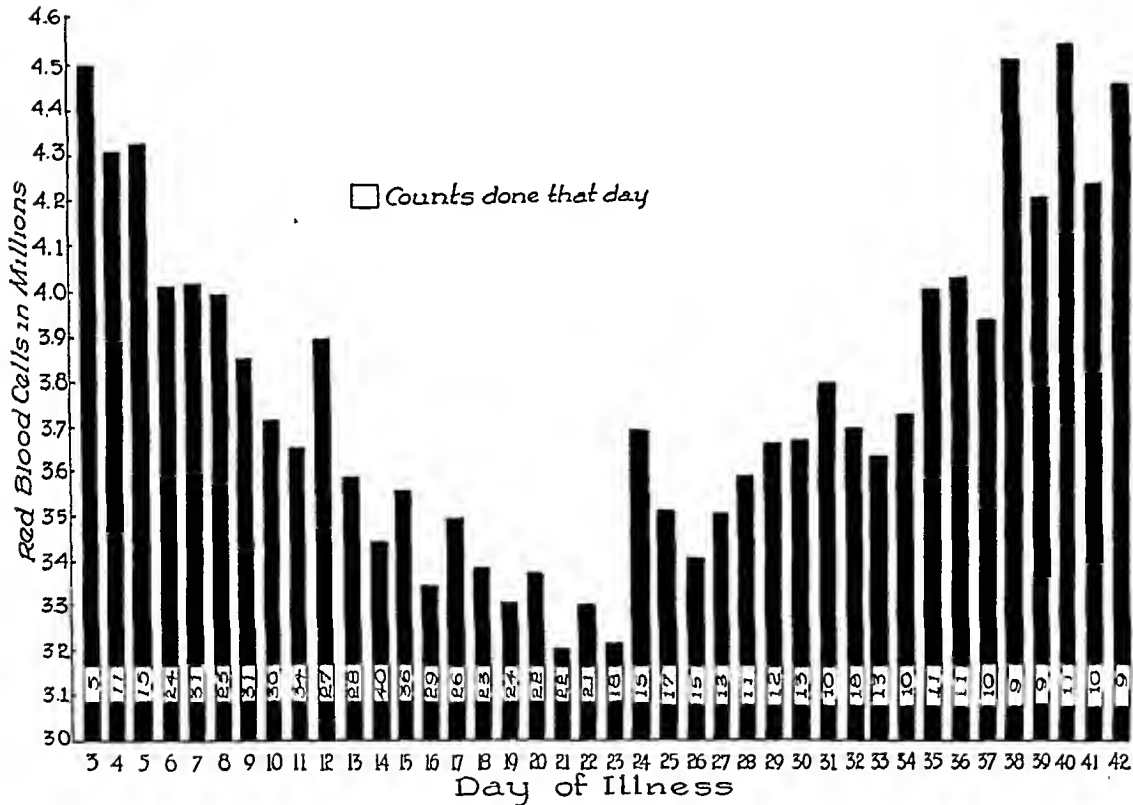


Chart 6.—Average red blood cell counts per day of illness of patients with uncomplicated typhoid, based on 749 determinations.

Urine.—Albuminuria was observed in 103 cases, an incidence of 28.61 per cent, in our series, and was usually transient in nature. Typically appearing late during the first week of illness, this transient albuminuria consistently cleared with convalescence. In a not inconsiderable number of these cases in which albuminuria occurred, casts, varying considerably in number and character, were also seen during the febrile course of the disease.

Serologic Examinations.—Serologic tests to determine the presence of syphilis were made routinely. In 11 cases the Kline and the Kolmer test were consistently positive, while in 3 instances (0.83 per cent) the serologic tests were positive during the febrile stage of the disease but became negative and remained so after defervescence occurred.

DIAGNOSIS

The diagnosis of typhoid depends on the demonstration of typhoid bacilli in the blood, the feces or the urine during some stage of the disease and on the development of a positive Widal reaction. When the disease is present in epidemic form, the clinical diagnosis may be strongly suggested by the symptoms presented, but even then it is necessary to have positive evidence of the nature of the disease in order to complete the diagnosis. It should be emphasized that a patient with typhoid, especially if seen after the fastigium is reached, is incapable of giving reliable historical data because of both the usually insidious onset and the increasing stupor, which makes it difficult to establish contact with the patient. Inadequate or unreliable historical information supplemented by a physical examination which fails to yield diagnostic information, then, is the problem which is too frequently encountered.

When one bears in mind certain characteristics of the disease, it is frequently possible to entertain a presumptive diagnosis of typhoid. Especially is this true during epidemics or in areas where cases of sporadic typhoid are known to occur. Typhoid is essentially an acute infectious disease, characterized usually by an insidious onset and a continued but gradual steplike rise in temperature, with a relatively slow pulse, which frequently becomes dicrotic unless a subsequent speeding-up of the pulse rate becomes manifest. Relatively severe headache, bronchitis, rose spots appearing in crops after the first week, splenic enlargement, leukopenia and anemia as the disease progresses and defervescence of the fever by lysis during the third or fourth week, when the various complications are oftenest seen, are also suggestive of typhoid.

Laboratory data derived from routine procedures other than the culture of blood, feces and urine and the utilization of the Widal reaction are not diagnostic of the disease. As previously shown (figs. 4, 5 and 6), leukopenia and anemia usually develop during the course of the disease. Albumin and casts are found in the urine of a not inconsiderable number of patients but are also evident among patients with other acute febrile diseases.

Of the specific laboratory procedures generally available, culture of the typhoid bacilli of the blood stream is by far the most conclusive proof of the nature of the disease. Especially is this true during the first week. In contradistinction, the Widal reaction, while of undisputed diagnostic aid, usually does not become positive until the second week of the disease, and sometimes even later, and in 34.17 per cent of our cases never reached a titer of significant diagnostic value (agglutination in a dilution of 1:160 or greater). Cultures of the feces and the urine, seldom revealing the presence of typhoid bacilli before the second or third week, may occasionally serve as conclusive proof of the

nature of the disease in question among cases in which the blood culture and the Widal reaction have failed, but they are certainly of more value in detecting those patients destined to become carriers of typhoid bacilli. .

Infrequently the diagnosis of typhoid is established only by post-mortem examination. This was true in 1 of our cases, an instance in which repeated cultures of blood, feces and urine as well as the Widal reaction were consistently negative. Characteristic ulcers of the distal portion of the ileum and of the ascending colon were considered, together with swollen, soft, hemorrhagic lymph nodes of the mesentery and a considerably enlarged spleen, to be pathognomonic of typhoid. This impression was further confirmed by later histologic examination of tissues which had been removed for study.

Although 245 of our patients (table 10) were admitted to the contagious disease unit of Charity Hospital with a provisional diagnosis of typhoid, approximately 100 of them had been patients in other

TABLE 10.—*Admission Diagnoses in Three Hundred and Sixty Cases of Typhoid, as Divided into Various Groups*

Admission Diagnoses	Number of Cases	Percentage
Typhoid.....	245	68.06
Other acute infectious diseases.....	38	10.56
Diseases of respiratory tract.....	32	8.89
Diseases of genitourinary tract.....	18	5.00
Diseases of gastrointestinal tract.....	13	3.61
Diseases of central nervous system.....	7	1.94
Miscellaneous diseases.....	7	1.94

Louisiana state hospitals for one or more days before being sent to the New Orleans institution and had, when first seen at this hospital, conclusive laboratory evidence of the disease. If one considers this fact, it becomes evident that an initial impression of typhoid, established at the time of the patient's admission to the hospital without the benefit of diagnostic laboratory information, was recorded for only 40 per cent of our series of patients.

The admission diagnoses, divided into groups of diseases, such as the acute infectious diseases and diseases with symptoms referring predominantly to various functional systems of the body such as the respiratory system, which included sinusitis, tonsillitis, bronchitis, bronchopneumonia and lobar pneumonia, are recorded in table 10. The differential diagnosis of these conditions is beyond the scope of this discussion.

It should, perhaps, be mentioned as a warning that the occurrence of the anamnestic reaction, the reappearance of the agglutinins due to inoculation after many years under the nonspecific stimulation of some

nontyphoid disease, may lead to an erroneous diagnosis of typhoid in an occasional case. On the basis that the typhoid bacillus contains two antigens, termed respectively O and H, it has been found that the agglutinins which appear in a previously inoculated person as the result of a subsequent nontyphoid infection are of the H and not of the O type. In contradistinction, if the O type can be demonstrated in the blood, it is proof that the infection belongs to the typhoid group. Certain it is, therefore, that bacterial suspensions containing the O type of antigen are to be preferred in performing the Widal test.

COURSE

The average duration of typhoid among our patients before entering Charity Hospital was ten days, but the time of admission varied from the second day of the onset to the early stages of convalescence. If account is taken of the temporary hospitalization of some of these patients at other Louisiana state hospitals, however, the average duration of disease before the patients entered the hospital was only nine days. The average duration of hospitalization of the surviving group of patients was forty days, including a few who reentered the hospital because of a relapse; whereas an average of about fifty days elapsed between the onset at home and the day of discharge from the hospital. The different manifestations of the disease have been described in detail, while the various complications, many of which have already been described, usually became apparent as the disease reached its maximum degree of severity or else at about the time that defervescence had begun.

COMPLICATIONS AND SEQUELAE

Complications that occurred during the course of the disease among the 360 patients of this series or became apparent as convalescence developed are shown in table 11. These complications, a total of 308, which included 29 individual conditions, were observed among 193 of these patients, whereas in only 167 patients (46.39 per cent) did one or more complications of the disease fail to develop. Two or more complications, not infrequently resulting in death, were commonly observed; patients showing an undesirable response to therapeutic agents were also listed in the group of patients with two or more complications.

Most of the complications have been described in detail, yet only the incidence, the average time required for fever to appear and the average duration of the fever as determined among the 45 patients experiencing a relapse have been described thus far. A true relapse, presumably due to an overflow of typhoid bacilli from previously established foci in the bone marrow, is but a shortened repetition of the original disease. Typhoid bacteremia was demonstrated by culture methods in 40 of these 45 patients, yet rose spots were apparent in but 16 patients. Reduplica-

tion of most of the manifestations of typhoid as found to occur during the original episode, but usually of lessened severity, was observed. Intestinal hemorrhages, of no great prognostic significance, were grossly evident in 3 cases, while but one relapse terminated fatally.

ASSOCIATED NONTYPHOIDAL CONDITIONS

Diseases that either were present before the onset of typhoid or were not considered attributable to typhoid are listed in table 12. Of these, heart disease of hypertensive, arteriosclerotic or syphilitic origin, with apparent evidence of cardiac failure developing in 10 patients, was probably the most serious. Six of 11 patients that had clinically

TABLE 11.—*Incidence of Complications Occurring in Three Hundred and Sixty Cases of Typhoid*

Complication	Number of Cases	Percentage
Gross intestinal hemorrhage.....	76	21.11
Bedsore.....	46	12.78
Relapse.....	45	12.50
Pneumonia.....	41	11.39
Obolecystitis.....	10	2.79
Cystitis.....	9	2.50
Furunculosis.....	8	2.22
Intestinal or appendical perforation.....	7	1.94
Psychosis.....	7	1.94
Carrier state.....	7	1.94
Pyelonephritis.....	7	1.94
Premature delivery or abortion.....	6	3.70*
Toxic myocarditis.....	6	1.67
Otitis media.....	5	1.39
Transient deafness.....	5	1.39
Venous thrombosis.....	3	0.83
Reaction due to sulfonamide therapy.....	3	0.83
Mastoiditis.....	2	0.56
Serum sickness due to antityphoid serum.....	2	0.56
Purulent parotitis.....	2	0.56
Toxic hepatitis.....	2	0.56
Typhoid meningitis.....	1	0.28
Typhoid endocarditis.....	1	0.28
Arterial thrombosis.....	1	0.28
Evisceration of abdominal contents following surgical abdominal examination.....	1	0.28
Purulent conjunctivitis.....	1	0.28
Transient paralysis of lower extremities.....	1	0.28
Flexion contraction of right hip.....	1	0.28
Periostitis of rib.....	1	0.28

* This percentage is calculated from the total number of women (162) in this series.

detectable heart disease failed to survive. Diabetes mellitus, severe in nature, proved difficult to control and was contributory to the death of 1 patient. Pregnancy, as previously mentioned, resulted in either premature labor or spontaneous abortion in every instance. Of interest, but fortunately of no prognostic significance, were the apparent examples of diseases due to contacts occurring during hospitalization. These included measles (3 cases), scarlet fever (2 cases) and chickenpox (1 case). None of the other associated diseases exhibited any apparent influence on the typhoid infection, nor did the latter seem to affect them to any appreciable extent.

DEATHS

Forty-six of 360 patients died of typhoid, a mortality rate of 12.78 per cent. Twenty-two were Negroes, and 24 were white patients; 27 were males, and 19 were females. The mortality rate among the Negro patients was 15.83 per cent, compared with 10.86 per cent among the white patients; this may be of some importance with regard to prognosis in the two groups. An analysis of the deaths that occurred in the various age groups (table 3) reveals death rates roughly proportional to the different age periods: The mortality of patients under 21 years of age was 6.44 per cent; the death rate among patients from 21 to 40 years of age was 19.7 per cent, and 28 per cent of the patients over 40 years of age succumbed to the disease.

TABLE 12.—*Incidence of Nontyphoidal Conditions in Three Hundred and Sixty Cases of Typhoid*

Nontyphoidal Condition	Number of Cases
Ascariasis.....	12
Syphilis, all varieties.....	11
Heart disease.....	11
Pregnancy.....	6
Essential hypertension.....	4
Measles during convalescent period.....	3
Scarlet fever during convalescent period.....	2
Diabetes mellitus.....	2
Sickle cell anemia.....	2
Inguinal hernia.....	2
Pulmonary tuberculosis.....	1
Malaria.....	1
Chickenpox during convalescent period.....	1
Diphtheritic vaginitis.....	1
Gonococcal urethritis.....	1
Pelvic inflammatory disease.....	1
Benign nephrosclerosis.....	1
Gastric ulcer.....	1
Bilateral nephroptosis.....	1
Mental deficiency.....	1
Perilicious anemia with posterolateral sclerosis.....	1

The average duration of the disease before death took place was 25.8 days. However, 1 patient with typhoid of an unusually malignant nature died on the twelfth day as a result of generalized peritonitis which followed the perforation of an ulcer located in the terminal portion of the ileum. The longest period of time from the onset of the disease until death occurred was sixty-three days. The patient, the only one to die among those suffering relapses, succumbed on the twenty-ninth day of the second febrile period, which was separated from the initial twenty-seven days of fever by seven afebrile days.

Autopsies.—Of the 46 patients who died in this series, only 18 (39.13 per cent) were submitted to postmortem examination. Except in 1 case in which proof of the nature of the disease was lacking at the time of autopsy, the diagnosis of typhoid was established in these cases as follows: In 9 instances a diagnosis was made by

isolating typhoid bacilli from the blood stream by cultural methods—in 6 by positive blood cultures and positive Widal reactions, in 1 by a positive agglutination test alone, and in 1 by isolating typhoid bacilli from the blood, the feces and the urine on culture mediums. Among the patients who died but who were not subjected to postmortem examination the diagnosis of typhoid was established on the basis of the following laboratory data: positive blood cultures in 7 cases, positive Widal reaction in 1 case and cultures of the stool and the urine yielding typhoid bacilli in 1 instance, while in each of the remaining 18 cases in which postmortem examinations were not made typhoid was indicated by the results of two or more of the specific diagnostic laboratory measures available.

Apparent Causes of Death.—Typhoid is a bacteremic disease, yet the intensity of the general symptoms, such as fever, headache and malaise is an indication of septicemia, the toxemia being due to the liberation of endotoxin that occurs when the bacilli are destroyed in the circulating blood. Twelve different complications or associated diseases considered capable of materially affecting the prognosis of typhoid in our patients occurred a total of sixty-two times among the 46 patients who died of typhoid. In contradistinction, 7 patients died in whom none of these complicating factors were evident, as well as 4 additional patients, each of whom had several days before death an episode of intestinal bleeding which was so mild in nature that it could not be considered as of more than casual significance. The deaths of 11 patients, then, were apparently due to the severe septicemic nature of the disease. Although postmortem examinations, which failed to disclose more than intestinal ulceration, splenitis and swollen, soft, hemorrhagic lymph nodes of the mesentery, were done on but 4 of the 11 patients, we are attributing these deaths (23.9 per cent) to the overwhelming toxemia and exhaustion which were manifested in these patients. Intestinal perforation, despite surgical intervention in all but 1 patient, was followed by general peritonitis in each instance and was the probable cause of death in 5 (10.87 per cent). Grossly evident intestinal hemorrhage occurred in 26 of these 46 patients who died, an incidence of 56.52 per cent, but 7 patients suffered loss of blood in such quantity and with such rapidity that complete exsanguination, rapidly followed by death, resulted. Intestinal complications, therefore, consisting of perforation in 5 (10.87 per cent) and fatal hemorrhage in 7 (15.21 per cent) were responsible for death in 12 of the 46 patients (approximately 26 per cent). Six patients (13.43 per cent of those who died) had some variety of preexisting heart disease which was the basis for the subsequent myocardial failure that deprived them of their life. A reaction following the administration of sulfathiazole, which included a cutaneous eruption, hematuria and oliguria, was the apparent

lethal factor in 1 patient, while severe diabetes mellitus which resisted all measures directed toward its control led to the death of another patient. Myocarditis, a result of the action of endotoxins liberated from destroyed typhoid bacilli and circulatory insufficiency, severe pyelonephritis and typhoid endocarditis were each responsible for a death among our patients. Evisceration of the intestines through a surgical incision, present as a result of a fruitless surgical abdominal exploration carried out eleven days before, and complete exsanguination due to frequent hemorrhages were jointly responsible for the failure of another patient to survive. Pneumonia, present in 15 patients, was the sole complicating factor in but 2 of these patients and usually was thought to be a part of the terminal picture rather than its cause. As to the remaining 7 patients who died, intestinal hemorrhage, cholecystitis, pneumonia, pleural effusion, hepatitis and benign nephrosclerosis were the pathologic conditions that, as a result of two or more of these conditions exerting deleterious influences on a single patient, hastened death.

PROGNOSIS

The death rate determined by an analysis of the 360 cases of typhoid included in this study was 12.78 per cent. It should, however, be mentioned that this figure is perhaps too high, as these patients, many of whom applied for hospitalization because of the grave nature of their illness, probably do not represent a fair sampling of the population with typhoid which included patients that did not seek hospital care—the typhoid in many of these patients probably being of a mild nature that was not reported. The death rate among the Negroes of this series was about 16 per cent, compared with less than 11 per cent among white patients. The prognosis of typhoid in children not more than 5 years of age as determined from 24 patients in our series, which included 2 infants of less than 1 year, was better than that of typhoid in any other age group large enough to be of possible statistical significance. The prognosis of typhoid as determined from this survey is appreciably graver among Negroes, among patients beyond 40 years of age, among persons with some chronic illness, e. g., heart disease, and obviously for any patient in whom ominous factors, such as toxemia and exhaustion, perforation, hemorrhage, pneumonia and other serious complications, are prone to occur.

TREATMENT

Symptomatic and Supportive Therapy.—Although preventive measures have produced a progressive decline in the incidence of typhoid in the United States, little progress in regard to treatment, as shown by a 12.78 per cent death rate in this series, has been recorded in recent years. Considerable investigation has failed to provide a specific

therapeutic agent with which to combat typhoid, although Reimann and his associates⁸ have recently discussed the administration of streptomycin to patients with typhoid and have reported favorable results in 3 of 5 patients treated with this agent. Treatment has, therefore, been directed toward providing general care, especially adequate nursing care and proper nutrition, yet a constant search for and prompt treatment of complications must be carried out. Prophylaxis, the prevention of the spread of infection to others, is also important and consists of such measures as prompt vaccination of all close associates of the patient, disposal of all excreta, care of linen and utensils and control of flies.

When typhoid is first suspected, the patient should be isolated and preventive measures should be utilized. The patient's room should be warm, well ventilated, quiet and screened. Rubber sheets, placed over a smooth mattress, and ordinary sheets, to be changed whenever soiled by the patient, aid in keeping the patient clean. Daily baths, supplemented by local cleansing after each bowel movement, are important, especially if followed by thorough drying and dusting with powders.

Bedsore, usually an evidence of pressure and uncleanness, are largely preventable. Oral hygiene, including use of suitable mouth washes, cleansing of the teeth and the gums and application of cold cream to the lips, is important in avoiding such complications as stomatitis, parotitis and otitis media and should be carried out by the nurse whenever necessary. Constipation, a frequent complaint, is often avoided by daily administration of small enemas whereas cathartics, especially the more vigorous ones, should be employed with caution, since hemorrhage or perforation may follow. Measures to reduce high temperature and delirium are of extreme importance. Tepid or cool sponging should be given every three or four hours to patients with a temperature of more than 102 F., unless the presence of some serious complication is suspected. Cold water enemas may be helpful in an occasional case when the temperature is unusually high. An ice bag applied to the head may furnish relief from headache. Distention, at times avoided by the use of a proper diet, is sometimes relieved by eliminating carbohydrates from the diet for a day or so. The giving of enemas, the use of turpentine stupes, the insertion of a rectal tube and the passage of a stomach tube are all measures directed toward the relief of flatulence. Diarrhea, at times controlled by alteration of the diet, may necessitate the use of opium and a bismuth preparation in small doses.

Dietotherapy.—Adequate amounts of fluids are necessary; they were administered parenterally to patients in our series who were comatose.

8. Reimann, H. A.; Elias, W. F., and Price, A. H.: Streptomycin for Typhoid: A Pharmacologic Study, *J. A. M. A.* **128**:175 (May 19) 1945.

During the period of high temperature 5 or 6 liters of fluid a day, including nutrient liquids, are mandatory. A liquid diet of about 3,000 calories a day, served in small feedings at frequent intervals, usually every two hours, is used at Charity Hospital. This diet, intended to maintain the patient's normal weight, provides sufficient bulk in the form of carbohydrates, with proteins and fat in proportion, to reduce the incidence of constipation. The constituents of the diet most frequently used, in addition to strained fruit juices supplemented with 10 Gm. of lactose, include cereal gruel with cream and sugar, eggnog made with boiled milk, strained soups, malted milk made with boiled milk, jello with whipped cream, custard, chocolate milk made with boiled milk and occasionally weak tea or coffee with cream and sugar. The diet should, however, be altered to suit individual tastes, and after convalescence is established, a low residue diet high in protein and calories is used. Transfusions of citrated whole blood were given to about half of our patients and were thought to be indicated whenever medical or surgical shock, profound anemia, inadequacy of blood proteins or toxemia with exhaustion were imminent.

In order to correct possible deficiencies, the administration of supplementary vitamins is frequently indicated in the dietotherapy of the patient with typhoid and this for several reasons. Though typhoid is an essentially self-limited acute disease, the basal metabolic rate during the febrile stages is elevated to 30 or 40 per cent above the normal values for that patient. In addition, the dietary intake may be inadequate as a result of nausea and vomiting, anorexia or even mental disturbances, e. g., delirium and coma. Absorption, too, is impaired because of diarrhea. Some believe that oral or parenteral use of 30 to 100 mg. of ascorbic acid and 2 mg. menadione (synthetic vitamin K) daily will offset the tendency to bleeding. Therapeutic dosages of the vitamin B complex may be indicated.

Reimann⁹ has outlined a satisfactory diet of 3,000 calories:

- 8 a.m.—Farina gruel: farina, $\frac{3}{4}$ cup; milk, $\frac{1}{2}$ cup; cream, $\frac{1}{4}$ cup; salt
Toast, 1 slice
Butter, 1 tablespoon
- 10 a.m.—Cocoa, 1 cup
- 12 noon—Milk toast: milk, $\frac{1}{2}$ cup; cream, $\frac{1}{4}$ cup; toast, 1 slice
Cream of pea soup, 1 cup
Egg, 1
Chocolate blanc-mange, $\frac{3}{4}$ cup
Butter, 2 tablespoons
- 2 p.m.—Malted milk, 1 cup
- 4 p.m.—Orangeade, 1 glass

9. Reimann, H. A.: Typhoid Fever, in Musser, J. H.: Internal Medicine, ed. 4, Philadelphia, Lea & Febiger, 1945, p. 28.

6 p.m.—Farina gruel, 1 cup
Milk, $\frac{1}{2}$ cup
Toast, 1 slice
Butter, $1\frac{1}{4}$ tablespoons
Egg, 1
Cup custard, $\frac{1}{3}$ cup
8 p.m.—Chocolate eggnog, 1 glass

Treatment of Intestinal Hemorrhage.—Absolute rest is necessary whenever intestinal hemorrhage is suspected or apparent. The stools should be examined closely for macroscopic or chemical evidences of blood, and determinations of blood pressure should be made at short intervals. Water may be given in small amounts, but food should be temporarily withheld. Opiates, which encourage flatulence, are best avoided, if possible, and should never be given until the question as to perforation has been answered. Morphine, in doses suitable to the individual patient, usually 0.015 Gm. ($\frac{1}{4}$ grain) in adults, is the preferable drug. Stools should be passed with the least possible effort, usually on a large pad. Transfusions of whole blood are of value when bleeding has been severe enough to produce an appreciable degree of exsanguination. Coagulants, used extensively among 76 patients with intestinal hemorrhage in this series, were of no noticeable value. Feeding was in most cases gradually resumed when indications of bleeding were no longer present.

Treatment of Perforation, Peritonitis and Other Complications.—Perforation and peritonitis call for surgical intervention. Repair of the perforation, done as promptly as possible, represents the only chance of recovery. In this series 2 of 6 patients that had intestinal perforations repaired at the time of operation recovered, while the other 4 died of peritonitis and abscess formation. Cholecystitis subsides spontaneously in most instances. None of our patients were subjected to surgical drainage during an acute episode. However, cholecystectomy was later performed, in 4 because of the persistence of typhoid bacilli in the bile. Other complications, such as venous or arterial thrombosis, parotitis, otitis media, mastoiditis, furunculosis, failing circulation and pneumonia, were combated with the therapeutic measures usually employed when one is dealing with these conditions.

Chemotherapy.—Various chemotherapeutic and biologic agents were given to many of these patients, either in an attempt to find some agent with specific action against the typhoid bacillus or because pneumonia or some other condition that might benefit from sulfonamide therapy was present. Aminopyrine and quinine were used extensively, often together, in many of the earlier cases, yet they were of little value. Their most appreciable contribution was a bizarre temperature curve. Specific typhoid antiserum, used in 5 patients, failed to exert a favorable

TABLE 13.—Comparison of One Hundred and Eleven Cases in Which Patients Were Given Sulfonamide Compounds with Two Hundred and Forty-Nine Cases in Which Patients Were Not Treated with Sulfonamide Compounds

Drug	Number Cases in Which Sulfonamide Drug Was Used	Duration of Disease Before Admission, Days	Duration of Fever,* Days	Time from Onset Until Discharge,* Days	Duration of Treatment, Days	Relapses		Intestinal Hemorrhages		Pneumonia		Deaths	
						Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Sulfanilamide.....	9	10.44	26.25	43.90	6.50	0	0.00	2	22.22	1	11.11	1	11.11
Sulfapyridine.....	23	8.74	30.77	50.83	9.40	3	13.04	2	8.70	8	34.71	1	4.35
Sulfathiazole.....	35	9.48	33.03	51.47	11.59	7	20.00	7	20.00	4	11.43	2	5.71
Sulfamethythiazole.....	6	9.80	27.20	41.00	12.50	0	0.00	1	16.67	0	0.00	0	0.00
Sulfadiazine.....	15	10.36	33.21	63.93	12.40	0	0.00	2	13.33	2	13.33	1	6.67
Absorbable group.....	88	9.56	31.38	52.69	10.69	10	11.36	14	15.91	15	17.05	5	5.68
Sulfaguanidine.....	8	6.50	60.25	82.25	10.00	4	50.00	0	0.00	0	0.00	0	0.00
Sulfasuxidine.....	8	9.25	37.00	67.50	11.50	0	0.00	3	37.50	0	0.00	0	0.00
Phthalylsulfathiazole.....	7	9.57	27.50	46.33	12.70	0	0.00	1	14.29	0	0.00	1	14.29
Nonabsorbable group	23	8.39	42.82	68.18	11.35	4	17.39	4	17.39	0	0.00	1	4.35
Treated group.....	111	9.31	33.75	55.89	10.83	14	12.61	18	16.22	15	13.51	6	5.41
Untreated group.....	249	10.44	29.17	47.28	0.00	31	12.45	58	23.29	26	10.44	40	16.06

* Cases in which death occurred are not included.

influence on the disease, while promin (sodium P, P'-diaminodiphenyl-sulfone-N,N'-didextrose sulfonate) was administered without apparent benefit to 4 patients. Not one of the sulfonamide drugs was used frequently enough to yield information of statistical value, yet 111 of our 360 patients received one of the eight sulfonamide compounds (table 13) in therapeutically significant doses for a period of five days or more. Further analysis reveals that 88 of the 111 patients treated with sulfonamide compounds received a drug readily absorbed from the gastrointestinal tract, while the remaining 23 were given drugs that are poorly absorbed from the intestine. Serious complications, e. g., pneumonia, were, if anything, more prevalent among the "treated" patients. None of the 5 patients who died of intestinal perforation received sulfonamide compounds. By far the most significant information derived from table 13 is that from a comparison of the death rates of the two groups: 5.41 per cent for the group treated with sulfonamide compounds and 16.06 per cent for the other patients of the series. Removal of the 5 patients with perforation from the statistical groups, in an effort to evaluate the two groups better, reduced the mortality percentage of the control group only to 14.34. The sulfonamide compounds used among these patients had no apparent effect on the typhoid bacilli present in the feces. The longer duration of fever and hospitalization among the group of 111 patients was due to the fact that 2 patients became carriers of typhoid bacilli after recovering from clinically apparent attacks of cholecystitis. Pneumonia was more prevalent in the group treated with sulfonamide compounds because pneumonia was used as an indication for chemotherapy in several instances. There was no significant difference in the number of relapses in the two groups. Perhaps by chance the incidence of intestinal hemorrhage was smaller in the smaller group, and possibly it had some bearing on the comparative death rates of the two groups. A sulfonamide drug reaction, mild in 2 patients, was seen in 3 of the 111 patients and was probably responsible for 1 death. Interpretation of these data regarding sulfonamide therapy in typhoid indicates that while the sulfonamide compounds do not affect the severity or the duration of the disease they are indicated whenever secondary infections, e. g., bronchopneumonia, occur. In that connection, penicillin may also prove to be of limited usefulness in the therapy of typhoid.

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LATENT PHASE OF ASIATIC SCHISTOSOMIASIS

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THE PURPOSE of this report is to describe the findings in the "latent" phase of infection with *Schistosoma japonicum* and to evaluate the treatment. The study is based on observations of 300 patients admitted to Harmon General Hospital approximately six months after the onset of their acute illness overseas.

On Oct. 20, 1944, and for several weeks thereafter, American troops landed on the east coast of Leyte, one of the Philippine Islands. These troops were engaged in, or supported, active combat during the wet weather of the northeast monsoons. Conditions of combat during this period necessitated fighting, working, wading or bathing in polluted fresh water streams and rice paddies which harbored the snails serving as the intermediate host of *S. japonicum*. The schistosomiasis is transmitted to the mammalian host by the cercarias, which penetrate into the capillaries of the skin and enter the venous circulation. These larvae are then carried to the right side of the heart, the pulmonary capillaries and thence to the left side of the heart and the systemic circulation. Those cercarias which reach the portal circulation mature, migrate to the venules of the mesenteric vessels and mate. Within a few weeks thereafter the females are laying ova.

In from three to nine weeks after the cercarias enter the body the early symptoms of the disease appear. These consist of chills, evening fever (temperature, 99 to 105 F.), headache, lethargy, backache, non-productive cough, abdominal discomfort and pronounced anorexia. In about one fourth of the patients in our series urticaria occurred at some time during the acute illness. Diarrhea developed in some and was neither bloody nor severe. Stupor, confusion, delirium and even paralysis, assumed to be due to the deposition of ova in the nervous system, developed early in a few patients. In rarer patients the constitutional symptoms were mild, and the diagnosis depended on the finding of ova in the stools. Enlargement and tenderness of the liver were common. The spleen was infrequently enlarged. Leukocytosis was usual, often

with an absolute eosinophil count as high as 20,000 per cubic millimeter of blood. The ova of *S. japonicum* were found first in the stools about seven and a half weeks after exposure.¹

REPORT OF CASES

CASE 1.—The patient landed on Leyte on Nov. 15, 1944. There were repeated exposures in fresh water subsequently. In the middle of January 1945, loss of appetite, abdominal cramps, diarrhea, feverishness and a slight cough developed. When the patient was hospitalized on February 27, the leukocyte count was 12,300, with eosinophils 20 per cent. The stools contained the ova of *S. japonicum*. The patient was treated with fuadin, 45 cc., with partial relief of symptoms. In May 1945, because of the finding of ova in the stools again and because of continued occasional epigastric cramps, he was again treated with fuadin, 45 cc.

The patient was evacuated to the United States, and on July 29 he arrived at Harmon General Hospital, essentially asymptomatic. Physical examination revealed no abnormalities except for slight tenderness in the right upper quadrant of the abdomen. The leukocyte count on admission was 7,750 per cubic millimeter, with eosinophils 8 per cent. On August 10 the stool was found to contain the ova of *S. japonicum*. The patient was treated with 416 cc. of a 0.5 per cent solution of antimony and potassium tartrate. This therapy was completed on September 20. Subsequent examinations of the stool have revealed no ova and the patient has remained free of symptoms.

CASE 2.²—The patient landed on Leyte on Oct. 20, 1944 and was repeatedly exposed by bathing and wading in fresh water until December 1. On December 19 he had a temperature of 103 F., night sweats, headache, lethargy, stiff neck, backache and diarrhea. Later loss of appetite developed. On December 25 he noted weakness of his hands, so that he had difficulty in buttoning his clothes. On Jan. 6, 1945 cough began. Two days later the patient became so confused that he was unable to find his way over familiar routes near his tent. The next day he was hospitalized. It was stated that he was "mentally retarded and had flaccid paralysis of his arms. The results of physical examination were otherwise negative." By the next day urinary incontinence had developed. The spinal fluid was normal. Repeated examinations subsequently showed definite weakness and spasticity of all extremities but more marked in the arms. The reflexes were all hyperactive. Confusion and irritability persisted. Lesions developed on his extremities, suggestive of the presence of emboli. On January 17 the ova of *S. japonicum* were first found in the stool, and the leukocyte count was 28,300 per cubic millimeter of blood with eosinophils 61 per cent. Fuadin, 50 cc., was administered. His general condition improved rapidly. No further treatment was given overseas.

On April 27 the patient arrived at Harmon General Hospital much improved. He complained of weakness, particularly of his upper extremities, and loss of the finer movements of the fingers. Physical examination of the abdomen revealed no abnormality. Neurologic examination demonstrated muscular weakness of the upper extremities, particularly the left, and hyperactive tendon reflexes throughout.

1. Thomas, H. M., and Gage, P.: Symptomatology of Early Schistosomiasis Japonica, Bull. U. S. Army M. Dept. 4:197-202 (Aug.) 1945.

2. The acute illness of this patient has been reported elsewhere (Johnson, A. S., Jr., and Berry, M. G.: Asiatic Schistosomiasis: Clinical Features, Sigmoidoscopic Picture and Treatment of Early Infection, War Med. 8:156 [Sept.] 1945).

The leukocyte count on admission was 16,400 per cubic millimeter of blood, with eosinophils 9 per cent. The spinal fluid was normal.

On August 3 the stools were again found to contain the ova of *S. japonicum*, and the patient was treated with fuadin 105 cc., the course being completed on September 18. Since then repeated examinations of the stools have revealed no ova. By the time the patient was transferred from Harmon General Hospital on November 12 his neurologic abnormalities had noticeably improved, although he still experienced some difficulty in driving a car. The tendon reflexes were still hyperactive, particularly on the left side, and there was minimal weakness of the left hand.

CASE 3.—The patient landed on Leyte on Nov. 15, 1944 and bathed repeatedly in fresh water streams. During a survey of the unit, routine blood smears during February and March showed eosinophilia (percentage, 50). He was hospitalized

TABLE 1.—*Common Symptoms and Physical Findings During Acute Phase of Infection with Schistosoma Japonicum in 300 Patients*

Finding	Patients	
	Number	Per Cent
Fever.....	266	89
Chill.....	153	50
Sweating.....	163	54
Headache.....	208	67
Lethargy.....	183	61
Myalgia.....	194	65
Rotary stiff neck.....	150	50
Dry cough.....	195	65
Urticaria.....	82	27
Anorexia.....	273	91
Abdominal pain.....	274	91
Diarrhea.....	148	50
Palpable liver.....	133	44
Palpable spleen.....	41	14
Jaundice.....	29	10
Tenderness in upper part of abdomen.....	285	95
Loss of weight (average, 25 lb. [11 Kg.]—range, 5 to 55 lb. [2 to 25 Kg.])	300	100

on March 31, 1945, although he had no symptoms other than slight cough and slight loss of appetite. After repeated examinations, on April 6 his stools were found to contain the ova of *S. japonicum* and he was given a course of 50 cc. of fuadin. The maximal percentage of the eosinophils in the white cell count during this period was 42.

On admission to Harmon General Hospital June 7 he was asymptomatic except for mild loss of appetite and "nervousness." Physical examination showed no abnormality. The ninth examination of the stools, on July 25, revealed the ova of *S. japonicum*. At this time the leukocyte count was 11,400 per cubic millimeter, with eosinophils 16 per cent. The patient was treated with 320 cc. of antimony and potassium tartrate. Subsequent stools on repeated examinations have contained no ova. The patient continues to be asymptomatic.

An analysis of the symptoms and findings recorded in the early stages of the disease in the first 300 patients admitted to Harmon General Hospital is presented in table 1. This information was obtained from the patients and from the complete overseas records returned to the United States with many of the patients. Some of these case histories

have already served as the basis for excellent reports by overseas observers³ and do not represent new data. They are presented in this paper largely for comparison with the findings on evaluation of the status of the patient's infection at the later phase of the disease when he came under our observation.

METHODS OF STUDY

On his admission to the hospital, each soldier gave a complete history and had a physical examination and certain laboratory tests. The hemoglobin content, the erythrocyte count, the erythrocyte sedimentation rate, the urinalysis and the non-protein nitrogen level of the blood were recorded in all cases. Electrocardiograms were made. Studies of hepatic function including the excretion of sulfobromophthalein, a cephalin flocculation test, a quantitative van den Bergh test, a determination of the icterus index and plasma protein partition were carried out. Cutaneous tests with an antigen prepared from *Schistosoma mansoni*⁴ were performed on most soldiers at different phases of the period of observation; the results will be reported separately.⁵ Each patient was examined with the sigmoidoscope, and the first 50 patients admitted had roentgenologic studies of the colon. In addition a schedule of the examinations of the stool was planned to give each soldier the benefit of at least eighteen examinations at intervals over a ninety day period. During the first two weeks following admission six specimens were examined. If these contained no ova and there were no other contraindications, the soldier was given a thirty day furlough. At the end of this period he returned for another evaluation and again had six stool examinations over a two week period. If no ova were found, he was placed on furlough for an additional period of twenty days. On his return for final evaluation six specimens of stools were examined. If the stools again contained no ova, the soldier was returned to duty to be reevaluated after three months.

At the time of the writing of this report 111 patients have been discharged from the hospital with a known number of persistently negative stools. The average period of observation for these patients was four months (range two and a half to five); the average number of stools examined per patient was twenty-two (range fourteen to thirty-five).

The stools of all patients were examined by multiple direct smears, and those of some, by concentration methods, such as sedimentation, ether extraction and zinc flotation. A comparison of the results obtained by these methods will be presented in a separate report.⁶ The direct smear technic detected six hundred sixty-three of six hundred and sixty-eight specimens of stool containing ova at the time of this analysis. A simple but time-consuming gravity sedimentation technic⁷

3. Billings, F. T.; Winkenwerder, W. L., and Hunninen: Studies on Schistosomiasis Japonica in the Philippine Islands, 1945, Bull. Johns Hopkins Hosp., to be published. Thomas and Gage.¹ Johnson and Berry.²

4. The *S. mansoni* antigen used was prepared by Mr. John Bozicevich and furnished through the courtesy of F. J. Brady, Surgeon, United States Public Health Service, the National Institute of Health.

5. Mitchell, L. P.: Skin Tests in Schistosomiasis Japonica, to be published.

6. Hesselbrock, W. B.; Lippincott, S. W.; Palmer, E. D.; Henderson, E. W., and Pauls, F. P.: Evaluation of a Serial Stool Examination Study in the Laboratory Diagnosis of Schistosomiasis Japonica, to be published.

7. United States War Department, Technical Bulletin (T B Med 167), Washington, D. C., Government Printing Office, June 1945.

used with one thousand and fifty-five specimens revealed only one third as large a percentage of the specimens containing ova as did the direct smear. In 2 of 42 patients the continued passage of eggs would, however, have been missed without the sedimentation technic. Although this is a laborious procedure, even a small increase in the specimens found to contain ova makes the procedure worth while, and adequate laboratory assistance should be available for its performance. In a small series of 29 cases in which a centrifugation-sedimentation technic⁸ was available for comparison with the direct smear and gravity sedimentation technics, 4 patients were found to have eggs in the stools by a combination of the latter two methods and 3 more were added to the group by adding the new technic to the other two.

The need for multiple examinations of the stools is indicated by the fact that, of all the patients found with ova in the stools at the Harmon General Hospital, only 17 per cent had ova at the time of the first examination and 13 per cent still had no ova at the completion of the tenth examination. In at least 3 cases, more than twenty stool specimens were examined at the hospital before the ova of *S. japonicum* were found. Furthermore, the stools of approximately 10 per cent of the patients who had ova in their stools were not found to have them until the final period of observation. This fluctuation in extrusion of ova is well known and indicates the need for prolonged follow-up with multiple examinations of the stool by multiple methods.

If the patient's stools were found to contain ova, treatment was started immediately with trivalent antimony. The subsequent period of follow-up before discharge from the hospital was planned essentially as previously outlined. In 47 of the 57 cases in which a patient was discharged from the hospital as "cured" after treatment, the average number of specimens of stools containing no ova obtained prior to discharge was nineteen (range ten to thirty-four) over an average period of three and a half months (range two and a half to four and a half). Because of the facts previously discussed, all patients discharged from the hospital were arbitrarily advised to have reexaminations made every three months for one year. Only if further data on these patients are collected both in military and in civilian life will it be possible to say whether or not this period of follow-up was adequate. The maintenance in the Office of the Surgeon General of a complete list of the names of the infected soldiers evacuated to this country will supply a first step toward proper organization of this follow-up.

CLINICAL EVALUATION OF THE STATUS OF THE PATIENT'S INFECTION ON ADMISSION

On arrival at Harmon General Hospital the patients appeared to be in strikingly good physical condition. This was attributed to the good care obtained in overseas hospitals during the acute phase of the disease and to the recuperative power of the young American soldier who had had only a limited number of exposures to the parasite. None of the patients was acutely ill, although residual complaints of a relatively mild degree were present in 85 per cent and stools containing ova were obtained from 31 per cent on the initial evaluation (table 2).

8. Technique for Examining Stools for Schistosomiasis Japonicum Eggs: Method of Lt. Barody, Moore General Hospital, Swannanoa, N. C., 1945.

Ova occurred in 30 per cent of the stools from patients with complaints and in 38 per cent of the stools from patients without complaints. This seems to justify the use of the term "latent" for this phase of the disease. The general condition of all patients was such that in only 6 instances did furlough have to be delayed beyond the initial two week period of evaluation. In these there were neurologic complications.

The abdominal symptoms, present in 156 of the 300 soldiers, were limited to the upper part of the abdomen. They varied from an indefinite soreness to intermittent mild to moderately cramping pain in the region of either the liver or the epigastrium. The abdominal tenderness in the same region varied from mild to moderate. In some, the complaints simulated those of patients with low grade cholecystitis, peptic ulcer or hepatitis. In a few instances histories were sufficiently suggestive to

TABLE 2.—*Symptoms and Findings on Initial Evaluation of the Status of Infection in 300 Patients at Harmon General Hospital*

Symptoms and Findings	Number of Patients	Number with Ova in Stools
Abdominal discomfort.....	156	
Weakness.....	75	
	255	
Other symptoms (headaches, myalgia, nervousness)....	186 (85%)	
No complaints.....	45 (15%)	17 (38%)
Palpable liver.....	32	
Palpable spleen.....	4	
Loss of weight.....	300 (100%)	93 (31%)
Total.....	300	93 (31%)

warrant roentgenologic studies of the gastrointestinal tract or the gall-bladder. None of these studies revealed abnormalities. The liver was palpable in 32 patients. In most of them it was barely palpable or was felt only a centimeter below the costal margin; in 1 patient it was palpable 3 cm. below the costal margin.

HEMATOLOGIC STUDIES

The relationship of the total white blood cell count and the maximal percentage of eosinophils to the findings in the stool is presented in table 3. It is seen first that during the latent phase of the disease the maximal total white blood cell count and the maximal eosinophil percentage were much lower than in the acute phase. During the early period of illness only 22 per cent of the patients had had maximal white cell counts less than 10,000 per cubic millimeter of blood, and only 6 per cent had maximal eosinophil percentages less than 9. In contrast, during the latent phase 64 per cent of the patients had leukocyte counts below 10,000 per cubic millimeter, and 50 per cent had eosinophil percentages below 9. During the acute phase, there was no correlation between the

height of the leukocyte count or the eosinophil and the percentage of patients with stools containing ova, approximately 75 per cent in each group. During the latent phase no patient had pronounced leukocytosis, and the moderate rises of the leukocytes to levels between 10,000 and 20,000 per cubic millimeter of blood were not associated with increased incidence of stools containing ova. In other words, although moderate and marked leukocytosis was a common feature of the acute phase of the disease, in the latent phase stools with ova were no commoner in those patients with leukocytosis than in those patients with normal cell counts.

Striking eosinophilia was also more characteristic of the acute than of the latent phase. Although there seemed to be some correlation

TABLE 3.—*Relationship of Hematologic Findings to Results of Examinations of Stools in Acute Phase (Overseas) and Latent Phase (Harlem General Hospital) of Asiatic Schistosomiasis*

Maximal Total Leukocyte Count	Acute Phase (Overseas)			Latent Phase (Harlem General Hospital)		
	Oases		Per Cent with Ova in Stools	Oases		Per Cent with Ova in Stools
	Number	Per Cent		Number	Per Cent	
5 - 10,000	65	22	72	192	64	32
11 - 19,000	130	45	70	105	36	34
20 - 29,000	71	25	79			
30 - 59,000	21	8	81			
Total.....	287	100		297	100	
Average.....			75			31
Maximal Percentage of Eosinophils						
0 - 9	17	6	88	148	50	20
10 - 29	62	22	69	119	40	41
30 - 49	75	26	73	25	9	56
50 - 69	92	32	71			
70 - 99	41	14	80	3	1	0
Total.....	287	100		295	100	
Average.....			75			31

between the level of the eosinophilia and the likelihood of finding ova in the stool during that portion of the latent phase represented by our initial evaluation, the number of patients with marked eosinophilia who had no ova in their stools on the initial evaluation prevent the use of a high level of eosinophilia, e. g., 30 per cent eosinophils, as a direct measure of continuing activity of the disease.

At the time when ova were first found in specimens of stools at the hospital, the average percentage of eosinophils for 140 patients was 14, with a fourth of the patients having 20 per cent or more. Four to six weeks after apparently successful treatment, however, the average percentage of eosinophils for 45 patients was 6, with none having more than 20 per cent. Four to six weeks after unsuccessful treatment, in 32 patients the average percentage of eosinophils was 10, with 2 having more than 20 per cent.

It is apparent that there is some tendency for the percentage of eosinophils to stay elevated when treatment has failed to eradicate ova from the stool. However, in individual patients apparently treated successfully and followed for a longer period of time there may be occasional transient eosinophilia with percentages above 20. Because of this variation in patients treated with apparent success, an occasional increased eosinophil percentage is of no particular diagnostic value. In any given case, however, a persistently elevated percentage should suggest a more diligent than usual search for ova.

Studies of the erythrocyte sedimentation rate on admission of the patients showed an incidence of 33 per cent stools containing ova in 219 patients with sedimentation rates of less than 10 mm. in one hour and 53 per cent in patients with rates above 10 mm. There were, however, only 39 patients in the latter group. The hemoglobin values and erythrocyte counts of almost all patients were normal on admission. Anemia had occurred in only a small percentage of patients during the acute illness and had been corrected prior to arrival in the United States.

STUDIES OF THE LARGE INTESTINE

Proctoscopic examination was made of the entire group of 300 patients. In only 3 were intestinal abnormalities found. They occurred as single flat oval granulomas, 0.5 to 2 cm. in their longest diameter and moderately indurated. These were 7, 10 and 15 cm., respectively, from the anus. They were well demarcated, and the low grade inflammatory appearance did not extend to the surrounding normal mucosa. The surfaces of the lesions were grayish pink and appeared roughened. Passage of the proctoscope over the lesion produced minute areas of oozing hemorrhage; a sense of induration and roughness was imparted through the proctoscope to the examiner's sense of touch. Biopsy and histologic sections showed the characteristic ova in the submucosa surrounded by chronic inflammatory tissue. In these 3 instances examination by direct fecal smear revealed ova; so the diagnosis of continued activity would have been made without proctoscopic examination. No elevated submucosal yellow nodules such as those described in the acute stage,⁹ or papillomas such as those seen in late stages,¹⁰ were observed in this group of patients in the early latent phase of the disease.

Roentgen examination after administration of a barium sulfate enema revealed no abnormalities of function or of structure of the colon in 50 patients who were thus examined.

9. An Aid in the Recognition of Schistosomiasis Japonica, Bull. U. S. Army M. Dept. 4:125 (Aug.) 1945.

10. Strong, R. P.: *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*, ed. 6, Philadelphia, The Blakiston Company, 1942, p. 1429.

FUNCTION OF THE LIVER

As a part of the initial examination, hepatic function was studied in approximately 250 of the patients. This seemed particularly indicated because of the symptoms in the right upper quadrant of the abdomen, the migration and final habitation of the parasite in the body, the occurrence of cirrhosis of the liver in repeatedly infected natives who were not treated, and the jaundice demonstrated or suspected in 10 per cent of the patients (table 1). It was also desired to use the results of the tests of hepatic function as a base line for studying the possible toxic effects of antimony on the liver. The following factors were measured: sulfabromophthalein retention, serum content of bilirubin, hippuric acid excretion, galactose tolerance and serum protein. In addition formaldehyde-gel tests were made. The detailed results will be submitted in a separate report; suffice it to say that on initial evaluation in this phase of the disease the percentage of patients with abnormal results was low. Of one hundred and forty-two initial determinations for 119 patients found to have stools containing ova at this hospital, 8 per cent showed sulfobromophthalein retention definitely increased (8 per cent or more). Of ninety-three determinations for 93 patients with stools containing no ova at this hospital, 13 per cent showed an increase of retention. Of the total of two hundred and thirty-five determinations, only 10 per cent showed 8 per cent or more retention. These abnormalities could not be correlated with the amount, the type or the date of previous treatment overseas.

Only 2 per cent of one hundred and thirty-two determinations of serum bilirubin in 129 patients with stools containing ova at this hospital showed 0.8 mg. per hundred cubic centimeters or more. Of one hundred and eighteen determinations for 118 patients with stools containing no ova at this hospital, 10 per cent showed an increase of bilirubin of this magnitude. These abnormalities could not be correlated with the amount, the type or the time of previous treatment overseas, but they did occur more frequently in those patients with abnormal retention of sulfobromophthalein than in those with normal excretion of this test substance. The other tests of hepatic function showed relatively few instances of definite abnormality and no correlation with the sulfobromophthalein or serum bilirubin tests. Evidence has been obtained, which will be presented separately,¹¹ that treatment with antimony and potassium tartrate may cause a transient disturbance of hepatic function.

Two patients in this series met accidental death while under observation. One had had repeated examinations of stools showing no ova over a period of five months prior to death. His liver was found sprinkled with miliary abscesses and fibrotic nodules surrounding schistosome ova. The total amount of liver tissue involved was small,

and the remainder of the organ was wholly unaffected.¹¹ The other, a patient who was under treatment with antimony and potassium tartrate because of ova in the stools, had had thorough studies of hepatic function with no evidence of impairment twenty-four days prior to death. His liver was similarly affected. How much damage of the liver will ultimately develop in this group of persons whose infection has been promptly diagnosed, who have been treated and removed from the endemic area, and who have been followed closely for failure of treatment and retreated if necessary is unknown. The natural course of the disease in untreated and frequently reinfected natives and the autopsy findings in the 2 cases reported make careful restudy of patients both in the army and in civilian life essential.

NEUROLOGIC STUDIES

The occurrence of neurologic complications during the acute phase of the disease has been previously reported.³ In 8 of the 481 patients considered at this hospital to have schistosomiasis there was frank evidence of neurologic disorder.

According to the overseas histories of these patients, neurologic manifestations first appeared during the acute phase of the illness and were most severe at that time. There were headaches, nuchal rigidity and mild mental symptoms of lethargy and confusion. In 3 patients there was a sudden onset of the full-blown syndrome of disseminated encephalomyelitis. In 3 others stupor developed. Among the 8 patients, cranial nerve abnormalities were noted in 6. These included diplopia, pupillary abnormalities and facial weakness. In all 8 there was evidence of involvement of the motor tracts of the spinal cord, with weakness and spasticity affecting one or more limbs. Paresthesias and sensory disturbances were noted in 3 patients.

When the patients whose studies had been completed were discharged from the military service, they had received maximal benefit from hospitalization. They had all improved, but none was completely free of the symptoms or signs of his neurologic disorder.

In 5 additional patients with schistosomiasis there were lesions suggestive of peripheral neuritis. Whether the neuritis was coincidental or whether it was due to the deposition of ova in peripheral nerves or their nutrient vessels is unknown.

RESULTS OF TREATMENT

Overseas.—The relationship of the type and the amount of drugs received overseas to the presence of ova in the stool on initial evaluation

11. Lippincott, S. W.; Paddock, F. K.; Rhees, M. C.; Hesselbrock, W. B., and Ellerbrook, L. D.: Liver Function Tests in Schistosomiasis Japonica with Particular Reference to Antimony Treatment with Reports of Two Autopsies, to be published.

in Harmon General Hospital is presented in table 4. It is seen that 36 per cent of the patients given fuadin overseas had ova in their stools on reevaluation, compared with only 12 per cent of those given antimony and potassium tartrate. No apparent relationship was found to the amount of antimony given, although the criteria for choice of the varying amounts could not be determined from the records.

Treatment at Harmon General Hospital.—At the suggestion of the Chief of the Tropical Disease Treatment Branch of the Office of the Surgeon General, patients with ova in their stools were given, in rotation and without regard to previous treatment overseas, equivalent amounts of antimony (0.57 to 0.58 Gm.) in the form of either fuadin

TABLE 4.—*Relationship of Drug Used Overseas to Initial Findings in Stools at Harmon General Hospital*

Drug Used Overseas	Approximate Amount of Antimony, Gm.	Total Number of Patients	Number with Ova in Stools, Overseas	Number with Ova in Stools, H. G. H.	Per Cent with Ova in Stools, H. G. H.
Fuadin, Cc.					
10 - 29.....	0.17	18	17	2	11
30 - 49.....	0.35	127	88	49	39
50 - 69.....	0.52	31	24	12	39
70 - 89.....	0.70	30	21	8	27
90 - 109.....	0.87	25	22	11	44
Total.....		231	172 (74%)	82	
Average.....					36
Antimony and Potassium Tartrate, Gm.					
0.5 - 1.0.....	0.27	6	3	1	17
1.1 - 1.4.....	0.45	3	3	0	0
1.5 - 1.9.....	0.61	25	21	3	12
Total.....		34	27 (8%)	4	
Average.....					12

or freshly prepared or commercially prepared antimony and potassium tartrate. Fuadin was given by injecting intramuscularly a 6.3 per cent solution on alternate days, beginning with doses of 1.5, 3.5 and 5.0 cc. and continuing with doses of 5.0 cc. until a total of 65 cc. had been given over a period of twenty-five days. Antimony and potassium tartrate, a 0.5 per cent solution, was given intravenously on alternate days, beginning with doses of 8, 12, 16 and 24 cc. and continuing with 24 cc. until a total of 320 cc. had been given in twenty-nine days. A complete record was kept of toxic symptoms by careful observation and daily questioning of patients. In addition, at a later date, 15 patients were treated with a course of 105 cc. of fuadin and 33 patients were given a course of 416 cc. of a 0.5 per cent solution of antimony and potassium tartrate.

The results of treatment are presented in table 5. The data indicate that antimony and potassium tartrate, either freshly or commercially

prepared, is far superior to fuadin in its immediate results, for 82 per cent of the patients treated with a single course of fuadin had ova in their stools again during the period of observation, compared with only 19 per cent of those given antimony and potassium tartrate.

Of those patients treated twice with fuadin, 69 per cent already have ova in their stools, although the follow-up period is not completed for any of them. Although no patients treated with the larger amounts of fuadin or of antimony and potassium tartrate have as yet again had ova in their stools, the follow-up period is too brief to justify conclusions. These patients are now being followed at another hospital.

The objection to the use of antimony and potassium tartrate in the past has been its reputedly greater toxicity as compared with fuadin. Over twenty-one hundred injections of a 0.5 per cent solution of antimony and potassium tartrate in a 5 per cent solution of dextrose

TABLE 5.—*Comparative Evaluation of Fuadin and Antimony and Potassium Tartrate in Patients Treated at Harmon General Hospital*

Drug	Amount of Antimony Given, Gm.	Number of Patients with Completed Evaluation Following Treatment	Number Whose Stools Contained No Ova During Follow-Up	Number Whose Stools Contained Ova During Follow-Up	Failures, per Cent
Fuadin (65 cc.), 1st course at H. G. H.....	0.57	33	6	27†	82
Antimony and potassium tartrate (320 cc.).....	0.58	59	48*	11§	19
Fuadin (65 cc.), 2d course at H. G. H.....	0.57	0	5†	11	69

* The treatment of 47 of these 48 patients was called a success, with an average of nineteen stools (range, ten to thirty-four) containing no ova over an average period of three and one-half months (range, two and one-half to four and one-half).

† The follow-up period has not yet been completed.

‡ The stools of 24 of the 27 patients again had ova when an average of seven stools (range, one to seventeen) had been examined over an average period of fifty-nine days (range, thirty-six to one hundred and eighteen days) after the completion of treatment.

§ The stools of 10 of these 11 patients again contained ova after an average of nine stools (range, eight to eleven) had been examined over an average period of seventy-eight days (range, forty-one to one hundred and four days) after completion of treatment.

|| The stools of 10 of these 11 patients again contained ova after an average of four stools (range, one to ten) had been examined over an average period of forty-four days (range, thirty-four to sixty-one) after completion of treatment.

in isotonic solution of sodium chloride have been given to 102 patients without serious reactions. The precautions taken at the time of administration were (1) that the patient be recumbent during the injection, (2) that the drug be given slowly (not faster than 8 cc. per minute) and (3) that the patient remain in bed for one hour after its administration. Only minor toxic symptoms were encountered, and their incidence is presented in table 6. It is seen that cough, either occasional or frequent, nausea or vomiting and muscle and joint pains occurred more frequently in the patients given antimony and potassium tartrate

than in those given fuadin. It is further seen that there was no difference in regard to incidence of symptoms when freshly prepared antimony and potassium tartrate was compared with the commercially prepared drug. The administration of antimony and potassium tartrate and fuadin in longer courses reaching larger total amounts of antimony was associated with a higher incidence of frequent muscle and joint pains.

The cough which appeared after the administration of antimony and potassium tartrate occurred in almost all the patients and usually lasted for one to five minutes, beginning immediately after the administration of the maximal dose of 24 cc. Transient muscular stiffness, especially in the shoulders, and transient joint pains usually developed during the latter half of the course of treatment. The stiffness of

TABLE 6.—*Percentage Incidence of Minor Toxic Symptoms of Antimony and Potassium Tartrate and Fuadin*

	Antimony and Potassium Tartrate				Fuadin		
	Fresh, 320 Cc.	Com- mercial, 320 Cc.	Fresh, 416 Cc.	Com- mercial, 416 Cc.	1st, 65 Cc.	2d, 65 Cc.	3d, 105 Cc.
Number of patients.....	36	33	17	16	33	25	15
Cough.....	69	58	76	81	0	0	0
Frequent cough.....	33	30	24	19	0	0	0
Nausea.....	17	15	18	13	0	4	0
Vomiting.....	6	6	6	0	0	4	0
Joint and muscle pain							
Occasional.....	81	52	24	13	6	28	0
Frequent.....	0	3	65	81	3	28	100

muscles generally developed in from six to eight hours after administration of the drug and usually lasted for from ten to twelve hours. Occasionally it persisted during the following day. Movement of the upper extremities involving active motion of the deltoid muscles produced distress. There was no muscular spasm or tenderness.

Therapy had to be discontinued in 2 cases because of the severity of the symptoms. In a patient who had previously had two courses of fuadin nausea, vomiting and dizziness developed even with reduced doses of the drug. He was subsequently given antimony and potassium tartrate, but the course of injections could not be completed because of the development of considerable stiffness of muscles and, at the eleventh dose, weakness, pallor and bradycardia. A second patient who was receiving antimony and potassium tartrate had his medication discontinued because of immediate vomiting and weakness even with a reduced dose. He subsequently took fuadin without difficulty. In the treatment of a third patient the use of antimony and potassium tartrate was stopped after the fifth dose because of the development of jaundice,

although this was thought to be infectious hepatitis rather than a drug reaction. Patients in whom tests of hepatic function showed mild impairment were treated with both antimony and potassium tartrate and fuadin without any immediately recognizable serious results.

For 66 patients receiving antimony therapy in the form of fuadin and antimony and potassium tartrate, electrocardiograms were made before treatment and one hour after the second, tenth and fourteenth doses of fuadin and after the fifth, twelfth and fifteenth doses of antimony and potassium tartrate. The alterations in the electrocardiograms were limited entirely to changes in the T waves. No changes occurred in any of the other segments. No disturbances of rhythm were found. In several instances a slight slowing of the rate was noted, but no rate below 60 was recorded. The abnormality consisted of varying degrees of depression of the T wave. This occurred in one or more leads. Thirty-one per cent of the patients receiving antimony and potassium tartrate and 7 per cent of those receiving fuadin exhibited either isoelectric levels or sharply negative and even cove-planed T waves in three or more leads, with low voltage in the remaining lead. These alterations might easily have been interpreted as evidence of myocardial damage or even have suggested coronary occlusion. Gradual return to normal began several days after cessation of therapy and was complete on reexamination after thirty days in 90 per cent of the patients.¹²

In view of the absence of evidence of serious cardiac or other significant toxicity, antimony and potassium tartrate in low concentration (0.5 per cent) appears to be the drug of choice as measured by the disappearance of ova from the stools. Since no differences were noted either in toxicity or in efficacy between freshly and commercially prepared antimony and potassium tartrate, the low cost of the former makes it preferable wherever the simple facilities necessary for accurate weighing and preparation of the solution are available.

CLINICAL STATUS ON COMPLETION OF PERIOD OF OBSERVATION

An analysis has been made of the records of 79 patients whose stools have remained free of ova of *Schistosoma japonicum* during three two week periods over an observation period of ninety days and of 15 patients whose stools similarly have contained no ova after completion of a single course of treatment at Harmon General Hospital. On completion of observation, approximately 90 per cent of the patients were free of symptoms, compared with only 15 per cent on admission (table 1). It is of interest that in a group of 71 patients whose stools were persistently free of ova at this hospital and whose records were available

12. Tarr, L.: The Effect of Antimony Compounds, Fuadin and Tartar Emetic, on the Human Electrocardiogram, Bull. U. S. Army M. Dept. 5:336 (March) 1946.

for analysis 42 per cent were symptom free at the end of their first furlough, approximately forty-five days after arrival here, compared with 15 per cent at the time of admission. However, the incidence of discomfort in the upper part of the abdomen which was 52 per cent at the time of the patients' admission was approximately the same at the time of their return from the first thirty day furlough. On completion of the observation period at the hospital, only 10 per cent of the patients had these complaints.

An analysis was made of the data on 92 patients who had completed a course of therapy and whose status had been reevaluated thirty days after completion of treatment. During treatment there was subsidence although not complete disappearance of symptoms. In many patients there was a gain of 3 to 4 pounds ($1\frac{1}{2}$ to 2 Kg.) in weight during treatment. During the thirty days of post-treatment furlough the patients began to experience the greatest relief of symptoms and to have a feeling of general well-being. Although the passage of time and the furlough itself contributed to this improvement, treatment was undoubtedly of importance. In general, the patients who received antimony and potassium tartrate were more commonly "symptom free," as a group, than those who had been given fuadin. It is difficult to say how much of this was conditioned by the rapidly spreading knowledge that a course of fuadin was less apt to free the stools of ova than a course of antimony and potassium tartrate.

COMMENT

Descriptions of Asiatic schistosomiasis¹³ are derived, for the most part, from observations of patients who continue to live and to be reinfected in endemic areas where they receive no or inadequate treatment. The organization for the care of American soldiers has been such as to hold exposure to the minimum consistent with military exigencies, to treat the disease promptly and to prevent further infection. The system of continuing care through the period in which the patient is evacuated from forward areas to the zone of the interior has given an exceptional opportunity to record observations on the course of the disease in persons removed from the possibility of reinfection. In Army hospitals observations will continue to be made on patients whose disease has been proved to be active, until apparent cure is achieved. Observations on patients discharged from the army as "cured" should continue into civilian life. The data reported permit a description of the status of a group of patients observed for at least three months, approximately four to nine months after infection.

13. Faust, E. C., and Meleney, H. E.: *Studies on Schistosomiasis Japonica*, American Journal of Hygiene, Monographic Series no. 3, Baltimore, 1924.

At the beginning of the observation period at Harmon General Hospital, none of the patients were acutely ill, and their general appearance was such that it seemed that a hopeful prognosis for recovery could be offered. Approximately half of them still complained of abdominal discomfort and one quarter of some weakness. With continued observation for a three month period the frequency of these complaints decreased still further, so that only 10 per cent of the whole group of 300 had residual symptoms.

In spite of the strikingly good clinical appearance of the men on their admission to Harmon General Hospital approximately one third of them had the ova of *S. japonicum* in their stools. This high incidence of continuing activity may have been associated with the use of fuadin overseas; for analysis of the failure of treatment both overseas and in the hospital indicated that much better results followed the use of antimony and potassium tartrate. Although a final evaluation of these drugs requires a longer period of observation than is now available, antimony and potassium tartrate seems unquestionably the drug of choice. Its reputedly greater toxicity has not been observed since adoption of the procedure of injecting a 0.5 per cent solution slowly. In order to obtain a better evaluation of the final results, all soldiers discharged from this hospital with stools repeatedly containing no ova have been advised to have quarterly reevaluation for one year. The point at which one is justified in pronouncing them "cured" remains to be determined.

This need for caution in pronouncing these patients "cured" gains emphasis from the paradox that even though the chief criterion for the diagnosis of activity of the adult worms is the finding of ova in the stools the disease must be thought of as a generalized systemic one. The generalization of the acute phase, the occurrence of embolic neurologic complications and the habitation of the ova-positing worms in mesenteric venules whence eggs may be swept to the liver, all point to the necessity of continued careful observation of these patients. This should be done with the thought of disclosing evidence of activity and of hepatic dysfunction.

SUMMARY AND CONCLUSION

An analysis has been made of the clinical and laboratory findings in a group of 300 soldiers admitted to Harmon General Hospital four to nine months after the onset of illness due to infection with *Schistosoma japonicum*.

Although on admission to the hospital the majority of them had residual complaints, e. g., abdominal discomfort, weakness, headaches, myalgia and nervousness, their general physical condition was excellent.

In spite of previous treatment overseas, approximately one third of the patients had the ova of *S. japonicum* in their stools when the initial evaluation of their status was made at Harmon General Hospital.

Treatment with antimony and potassium tartrate (320 cc. of a 0.5 per cent solution) and fuadin (65 cc. of a 6.3 per cent solution), containing equivalent amounts of trivalent antimony (0.58 Gm.) resulted in the disappearance of ova from the stools in 81 and 18 per cent of the patients, respectively, during a period of follow-up averaging approximately three months. Since no major toxic effects were encountered with antimony and potassium tartrate in the concentration employed, it is clearly the drug of choice.

There is need for continuing a careful follow-up of these patients.

ADDENDUM

Since this paper was submitted for publication a continuing opportunity has been afforded to study the results of various treatment schedules. The evidence at present indicates that 444 cc. of a 0.5 per cent solution of antimony and potassium tartrate, U. S. P., is the most effective therapy. This is given intravenously on alternate days, beginning with 8 cc. and increasing the dose 4 cc. with each dose until a maximal dose of 28 cc. is given. The dose of 28 cc. is repeated every other day until 444 cc. (2.2 Gm.) of antimony and potassium tartrate has been received.¹⁴

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14. Most, H.: Personal communication to the authors.

CLINICAL NEPHROPATHIES IN EARLY SYPHILIS

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SYPHILITIC involvement of the kidneys, especially in early syphilis, has long been recognized. But the manifestations of a genuine syphilitic nephrosis or nephritis are so infrequent that even those who specialize in renal diseases may be confused by their occurrence. Because of this, it seems worth while to report our experience with syphilitic nephropathies at Bellevue Hospital. We have reviewed all of the cases of secondary syphilis treated in the wards of the hospital since January 1940. All of these patients were given some type of rapid treatment for syphilis. Twelve, or less than 0.3 per cent of those treated for secondary syphilis, showed markedly abnormal urinary findings which responded rapidly and dramatically to intensive, rapid treatment for syphilis. Ten of the 12 were girls or women. The cases are in accord with the description of early syphilitic nephropathies found in the literature. We have omitted from this report all instances of mild albuminuria prior to treatment.

One of the most comprehensive papers on clinical syphilitic nephropathies was written by Herrmann and Marr¹ in 1935. In 1934 Wosika and Thurmon² reported on syphilitic albuminuria. In later years reports have been made in this country by Baker,³ Patton and Corlette,⁴ and Klein and Porter.⁵ Spanish and South American journals have

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1. Herrmann, G., and Marr, W.: Clinical Syphilitic Nephropathies, *Am. J. Syph. & Neurol.* **19**:1, 1935.

2. Wosika, P. H., and Thurmon, F. M.: Syphilitic Albuminuria, *Am. J. Syph. & Neurol.* **18**:2, 1934.

3. Baker, B. M., Jr.: The Relation of Syphilis to Nephritis, *Bull. Johns Hopkins Hosp.* **65**:196, 1939.

4. Patton, E. W., and Corlette, M. B.: Three Cases of Acute Syphilitic Nephrosis in Adults, *Ann. Int. Med.* **14**:1975, 1941.

5. Klein, A., and Porter, W. B.: Nephrosis Associated with Early Active Syphilis, *South. M. J.* **36**:694, 1943.

(Footnotes continued on next page)

published several articles on the same subject in recent years.⁶ Both Stokes⁷ and Moore⁸ gave brief accounts of renal involvement in early syphilis and there can be no doubt that it occurs.

Herrmann and Marr¹ made an elaborate classification of early and late syphilitic nephropathies which is possibly more theoretic than real. But, if one chooses to label under separate headings every variety and degree of renal manifestation seen in early syphilis, an elaborate outline may be needed. With respect to the urine alone, early syphilitic nephropathies may simulate almost any known type of renal disease with the exception of pyogenic infections. When it comes to late syphilitic renal disease, we can say nothing because during the past ten years no patient has come to our attention for whom the diagnosis could be made. Such cases have been reported in the literature and, in view of the pathologic findings in kidneys of 19 patients with syphilis, described by Rich¹⁹ in 1932, it is possible that late syphilitic nephropathies occur more frequently than we recognize them. We are at a loss, however, how to make the diagnosis unless manifestations of renal disease in late syphilis respond to antisyphilitic treatment. Such manifestations in our experience have been conspicuous by their absence.

CLINICAL MANIFESTATIONS OF EARLY SYPHILITIC NEPHROPATHIES

The urinary findings in early syphilitic nephropathies may vary from a mild albuminuria with few unusual elements in the sediment to a tremendous albuminuria associated with a few or a large number of casts. Red blood cells may be absent during the entire period of observation, or they may vary in numbers from an occasional cell to almost a gross hematuria. Because of this, early syphilitic nephropathies have usually been divided into syphilitic nephritis and syphilitic nephrosis. In our own experience the latter is commoner, but it is doubtful whether any distinct line can be drawn between the two in some cases.

NEPHROSIS IN SECONDARY SYPHILIS

The usual picture of early syphilitic nephrosis consists of a marked albuminuria, from 10 to 30 Gm. having been reported in twenty-four hour specimens. Some degree of oliguria is commonly associated

6. Luque, J. D.: Nefropatía sifilítica en el lactante, *Rev. chilena de pediat.* **14**:688, 1943. da Silva Mello, A.: Nefrites crônicas sifilíticas; um grupo autônomo de nefrites, *Rev. brasil. med.* **1**:16, 1944. Jiménez Diaz, C.: La sífilis renal, *Rev. clín. españ.* **9**:145, 1943.

7. Stokes, J. H.; Beerman, H., and Ingraham, N.: *Modern Clinical Syphilology*, ed. 3, Philadelphia, W. B. Saunders Company, 1944, p. 603.

8. Moore, J. E.; Kemp, J. E., and others: *Modern Treatment of Syphilis*, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1941.

9. Rich, A. R.: Pathology of 19 cases of Nephritis Associated with Acquired Syphilis, *Bull. Johns Hopkins Hosp.* **50**:357, 1932.

with the albuminuria. The urine sediment contains casts but few or no red blood cells and the cylindruria is less noticeable as a rule than in cases of lipid nephrosis due to other causes. Renal function is rarely impaired to any great extent. Mosenthal and Volhard tests usually show that the kidneys can concentrate and dilute the urine within normal limits, but elimination of the urine may be delayed. The nonprotein nitrogen content of the blood is not above normal. There may be some impairment of the urea clearance and the excretion of phenolsulfonphthalein. As a rule the patients complain of no subjective symptoms and, unless edema is present, the diagnosis is suspected only if routine urine examinations are made, and it is confirmed by the rapid disappearance of abnormal findings when antisyphilitic treatment is given.

Ten of the 12 cases reviewed by us were classified as belonging in the nephrosis group rather than that of nephritis. This decision may have been somewhat arbitrary. It was based on the predominating albuminuria with the presence of only a few or no red blood cells. In all but 3 patients, red blood cells ranging from an occasional cell to 7 or 8 in a high power field were reported at some time during the course of the involvement. Waxy casts were reported in 7 of the patients at the time of admission to the hospital. In no case was the blood pressure elevated. None had a secondary anemia and only 2 had any complaints referable to renal disease when admitted to the hospital. One complained of a dull headache associated with dizziness of two days' duration. The other stated that she had not voided in over twenty-four hours. When she was catheterized, 1,100 cc. of urine was obtained. The albumin formed a solid clot when the urine was boiled in a test tube, and numerous waxy casts were seen on microscopic examination.

In view of the presence of a few red blood cells in the urine of 7 of the patients in this group it is apparent that the glomeruli as well as the tubes are usually involved in the syphilitic process. As a matter of fact the urinary findings might suggest in some cases the nephrotic type of glomerulonephritis. Against this diagnosis is the relatively good renal function and the absence of much edema, although the latter has been reported in cases of secondary syphilitic nephrosis in the literature. All 10 of the patients observed by us were able to dilute and concentrate the urine within normal limits. None had more than 30 mg. of nonprotein nitrogen per hundred cubic centimeters. Urea clearance tests were done in 3 cases with only mild or no changes from normal findings. The plasma proteins were also within normal limits with normal albumin-globulin ratios. Excretion of phenolsulfonphthalein was only slightly diminished. The urinary findings became normal within four to eight days in every case. All 10 patients received rapid treatment for early syphilis. One received oxophenarsine hydrochloride alone. Six received daily injections of 0.06 Gm. of oxophenarsine and

fever was induced four times in ten days by the intravenous injection of typhoid vaccine. Three received penicillin, individual injections being given every three hours for sixty doses. One had a Herxheimer reaction with a temperature on the first day of treatment up to 104 F., but the urinary findings improved on the following day in spite of this. In no case was antisyphilitic treatment started with small doses of arsenical drugs or of penicillin because of the danger of a Herxheimer reaction. Therefore, from our experience, there is little to fear from Herxheimer reactions in secondary syphilitic nephrosis.

Because of the similarity of findings in these cases, there seems to be little reason to take the space or bore the reader with case histories of all 10. We have chosen 1 case for a detailed history, which follows:

REPORT OF A CASE

M. L., a 20 year old unmarried Negro woman, was admitted to Bellevue Hospital on Dec. 27, 1942. On admission her only complaints were a generalized rash associated with a sore throat of about two weeks' duration. Her past history included hay fever, which she reported having had in late July and August every summer since she was 9 years of age. In September 1940 she had a Bartholin cyst which was treated at Harlem Hospital. Her blood Wassermann reaction at that time was reported as negative. Her menstrual periods had been regular, the last regular period having ended about December 8. She stated that she noted vaginal bleeding again on December 25, but this stopped after one day.

On physical examination she did not appear acutely or chronically ill. She was well nourished. She had a generalized maculopapular rash on the face, trunk and extremities with numerous moist papules on the vulva. There were no mucous patches in the mouth or the throat, but the pharynx, pillars and tonsils were diffusely reddened. The eyes were normal except for a pigmented patch in the left fundus, due to an old traumatic chorioretinitis. Generalized adenopathy was present. The lungs were clear. The heart was normal in size and shape. The heart sounds were of good quality. No murmurs were present. The blood pressure on admission was 105 systolic and 70 diastolic, the highest reading throughout her stay in the hospital having been 124 systolic and 80 diastolic. The abdomen was not tender, and the liver and the spleen were not palpable. All deep reflexes were present. Vaginal examination showed some erosion of the cervix.

Laboratory Data on Admission.—Dark field examination of serum from the moist papules on the vulva showed many *Treponema pallidum* organisms. Smears for gonococci from the urethra and the cervix were negative. The blood Wassermann and Kahn reactions were strongly positive. The results of the urinalysis on December 28 were reported as follows: reaction, acid; specific gravity, 1.018; albumin (4 plus); sugar, none. Microscopic examination of the urine revealed many coarsely granular casts and numerous waxy casts, occasional white blood cells and 2 to 3 red blood cells per high power field. The blood cell count on the same day was: hemoglobin (Sahli), 80 per cent; red blood cell count, 4,180,000; white blood cell count, 13,600, with 63 per cent polymorphonuclear cells, 24 per cent lymphocytes and 1 large mononuclear cell. Results of an examination of the spinal fluid on December 30 were as follows: cells, 2 to 3 per cubic millimeter; amount of globulin, normal; total protein, 10 mg. per hundred cubic centimeters; Wassermann reaction negative, and gold curve, normal.

Course.—After the diagnosis of secondary syphilis, the patient was started on rapid antisyphilitic treatment with oxophenarsine hydrochloride. Our plan of therapy at that particular time called for two intravenous injections of 0.07 Gm. oxophenarsine hydrochloride each day for eight days. The patient was given two such injections on December 31. Then, as the urine report still showed a large amount of albumin and a few red blood cells per high power field, antisyphilitic treatment was stopped until a consultation could be obtained from the renal disease service of the medical department. It is unfortunate that the patient received some treatment prior to a thorough renal examination, because the latter was not obtained for several days after treatment was started and stopped. The abnormalities of the urine did not clear up rapidly after the two injections of oxophenarsine hydrochloride, but improvement was noted by the time the following laboratory data were obtained, three days after treatment was stopped.

Urea clearance was 95 per cent. The report on the urinalysis made on the same day was as follows: reaction, acid; specific gravity, 1.018; albumin (3 plus); sugar, none. Microscopic examination revealed numerous granular casts, numerous white blood cells and 1 to 2 red blood cells per high power field.

The nonprotein nitrogen of the blood was 20 mg. per hundred cubic centimeters. Results of the congo red test were negative. The plasma proteins were as follows: total protein, 6 Gm.; albumin, 3.2 Gm., and globulin, 2.8 Gm. per hundred cubic centimeters. Results of Mosenthal tests were within normal limits.

Antisyphilitic treatment with two injections of 0.07 Gm. oxophenarsine hydrochloride daily was resumed on January 7 and continued without interruption until the patient had received a total of sixteen injections. By the time that treatment was completed the urine was entirely free from albumin. The plasma proteins at the end of treatment showed a total protein of 6.6 Gm., the albumin being 4 Gm. per hundred cubic centimeters and the globulin 2.6 Gm. The nonprotein nitrogen of the blood was 17.2 Gm. per hundred cubic centimeters, and the urea clearance was 127 per cent when treatment ended.

On January 9 the patient was discharged for follow-up in the outpatient department, where subsequently the urine was found to be normal.

NEPHRITIS IN SECONDARY SYPHILIS

The chief distinction between early syphilitic nephritis and nephrosis is the relatively mild or moderate degree of albuminuria and the relatively pronounced hematuria in the former. We have classified 2 of our cases in the nephritis group. One of them simulated the focal type of glomerulonephritis rather than diffuse glomerulonephritis. The patient was a 19 year old Negro who had a fairly pronounced hematuria with innumerable red blood cells in every high power field on microscopic examination of the urine sediment. He had only a moderate albuminuria, the specimens examined before treatment being reported as giving a 2 plus reaction for albumin. Numerous granular casts were also reported. He had no hypertension or anemia and no subjective complaints. Renal function was not significantly disturbed. Antisyphilitic treatment with daily injections of 0.06 Gm. oxophenarsine hydrochloride and fever induced four times by typhoid vaccines, in a treatment period of ten days, reversed the urinary findings to normal.

The other patient was a young Negro girl who had what appeared to be a typical attack of diffuse glomerulonephritis which at first we believed was not due to syphilis. She had both hypertension and secondary anemia, together with moderate albuminuria and mild hematuria. Significant changes in the renal functions were also present.

The great improvement following penicillin therapy for secondary syphilis caused us to change our minds about the diagnosis. The case report follows:

REPORT OF A CASE

E. G., a 14 year old Negro girl, was admitted to Bellvue Hospital on Sept. 9, 1944. The past history was negative for renal disease or any other serious illnesses. About one month prior to admission she had been taken to Harlem Hospital because of pain in the lower part of the abdomen. From Harlem Hospital she was transferred to City Hospital, where diagnoses of gonorrhea and secondary syphilis were made. At City Hospital she received 20 Gm. of sulfadiazine for gonorrhea and three injections of oxophenarsine hydrochloride, 0.01 Gm., 0.02 Gm. and 0.04 Gm., respectively. She was then transferred to Bellevue Hospital for treatment with penicillin.

The physical examination, on admission to Bellevue Hospital, revealed a fading papular rash on the trunk and extremities with papules on the palms and soles. Generalized adenopathy was present. There was some tenderness in both lower quadrants of the abdomen. Otherwise the examination revealed no abnormalities except for a blood pressure of 180 systolic and 120 diastolic.

Laboratory Data.—The report on the urinalysis on the day following admission was: reaction, acid; specific gravity, 1.016; albumin (2 plus), and sugar, none. The microscopic examination revealed numerous granular casts and occasional hyaline casts; 50 to 70 white blood cells and 25 to 50 red blood cells per high power field. Similar findings were reported for the next seven days, during which time no antisyphilitic treatment was given and no sulfonamide drugs. Cultures for gonococci from the cervix and urethra were negative. The blood Wassermann and Kahn reactions were strongly positive. The nonprotein nitrogen of the blood on September 11 was 30 Gm. per hundred cubic centimeters. A blood count on the same day gave the following results: hemoglobin 9.3 Gm.; red blood cells, 2,970,000, and white blood cells, 9,600, with 68 per cent polymorphonuclear cells. The lowest specific gravity of the urine in Volhard tests was 1.004, and the highest 1.021. The rate of excretion was diminished (580 cc. in five hours after an intake of 1,500 cc. of water).

Course.—In view of the above observations, a diagnosis of diffuse glomerulonephritis was made. On September 15 treatment was started with penicillin; the patient received 20,000 Oxford units every three hours for sixty doses, over a period of seven and a half days. Daily determinations of blood pressure and urine-analyses were done throughout treatment, and Volhard tests were repeated during treatment and again on September 25. To our surprise definite improvement began to occur toward the end of treatment with penicillin. The blood pressure readings from the day preceding the onset of therapy to the time of discharge are as follows: September 14, 205 systolic and 140 diastolic; September 15, 170 systolic and 110 diastolic; September 16, 170 systolic and 120 diastolic; September 19, 185 systolic and 120 diastolic; September 20, 155 systolic and 100 diastolic; September 21, 160 systolic and 100 diastolic; September 22, 158 systolic and 100 diastolic; September 24, 145 systolic and 100 diastolic; September 26, 140 systolic and 90 diastolic;

September 27, 130 systolic and 82 diastolic; October 1, 115 systolic and 70 diastolic; October 2, 124 systolic and 70 diastolic; October 4, 120 systolic and 80 diastolic, and October 17, 120 systolic and 75 diastolic. Urinalysis showed similar improvement, both the albuminuria and sediment abnormalities clearing up, the hematuria having disappeared entirely by September 22, the last day of penicillin therapy. There was also improvement in the elimination and concentration tests.

The patient was discharged on October 18, at which time her blood pressure was normal and the urine showed only a trace of albumin with no casts. She was observed irregularly after her discharge, but on subsequent visits the blood pressure and urine were normal and the anemia improved. She was readmitted to the hospital on June 18, 1945, because of another attack of gonorrhea, for which she was treated with 150,000 units of penicillin. At that time her blood pressure was 125 systolic and 80 diastolic, and daily urine specimens examined from June 18 to June 27 were normal except for a faint trace of albumin.

DIFFERENTIAL DIAGNOSES

Obviously the diagnosis of a syphilitic glomerulonephritis was doubtful when the second patient whose case is reported was admitted to the hospital. It is still possible that syphilis may not have been the true cause of her nephritis. Nevertheless, in view of the course of the illness, we are unable to make any other diagnosis than that of glomerulonephritis due to secondary syphilis.

In contrast to this case, we have observed in 3 cases that glomerulonephritis was present at the time when the patients were given a diagnosis of secondary syphilis. None of these responded well to anti-syphilitic therapy. One of them was treated with oxophenarsine hydrochloride and fever induced by typhoid vaccine without any appreciable exacerbation of the glomerulonephritis, but the patient continued to show the same manifestations during treatment and for some months thereafter, until he was lost from observation. He had a hypertension which persisted as did his mild albuminuria and hematuria. The other 2 were cleancut cases of diffuse glomerulonephritis. Both were treated with penicillin for secondary syphilis without any change in the renal function or urinary findings. In these cases secondary syphilis and nephritis were independent of each other.

Certainly, in the absence of hypertension and a history of previous renal disease, even a pronounced hematuria associated with secondary syphilis should be suspected as being due to the syphilis, but no certain diagnosis can be made prior to antisiphilitic treatment. The rare cases of secondary syphilitic nephritis were a real problem prior to the advent of penicillin. Today, however, such patients can be treated with relative safety by the use of penicillin. When a marked hemorrhagic nephritis is present, probably small doses of spirocheticidal drugs should be used initially to avoid a Herxheimer reaction. In the cases of milder disease, however, we have seen no cause for alarm in starting penicillin with doses of 20,000 to 40,000 Oxford units dissolved in water. Secondary

syphilis is almost never destructive and leaves no scar tissue as a rule. No sequelae have ever been reported for secondary syphilitic involvement of the kidneys, so far as we know.

The nephrotic type of involvement which has been observed by us is much more readily ascribed to secondary syphilis than the type simulating glomerulonephritis due to other causes. The noticeable albuminuria found in the former should in itself suggest the correct diagnosis. Prior to the advent of penicillin, when we treated large numbers of patients having early syphilis with arsenical drugs and fever induced by typhoid vaccine, albuminuria and sometimes hematuria occurred occasionally as reactions to the treatment. The urinary abnormalities were transitory and cleared up rapidly when treatment was stopped. The differential diagnoses between such reactions to treatment and urinary abnormalities due to syphilis is of course easy when the urine is reported normal prior to the onset of treatment.

In a previous publication¹⁰ we reported several severe renal reactions which occurred following prolonged fever treatment produced by electropyrexia in combination with oxophenarsine hydrochloride. In these cases renal function was severely impaired, although fortunately all the patients recovered with no apparent sequelae.

SUMMARY

Early syphilis may involve the kidneys, simulating a nephrosis or glomerulonephritis. Of 12 cases of renal involvement in secondary syphilis reported, 10 were classified as syphilitic nephrosis and 2 as nephritis. In syphilitic nephrosis results of tests of renal function are not significantly abnormal as a rule, but pronounced albuminuria and cylindruria are present. In early syphilitic nephritis, there is less albuminuria than in nephrosis and more hematuria. In 1 case of diffuse glomerulonephritis apparently due to secondary syphilis, in which there was hypertension and secondary anemia, there was response to anti-syphilitic treatment with penicillin. Early syphilitic nephropathies leave no demonstrable sequelae.

10. Thomas, E. W.; Wexler, G.; Schur, M., and Goldring, W.: Acute Nephrosis Complicating Two Day Arsenic and Fever Therapy for Early Syphilis, *J. A. M. A.* **122**:807 (July 17) 1943.

ASSOCIATION OF PNEUMONIA WITH ERYTHEMA MULTIFORME EXUDATIVUM

COMMISSION ON ACUTE RESPIRATORY DISEASES *

FORT BRAGG, N. C.

THE BENIGN form of erythema multiforme exudativum (Hebra) is a familiar condition in medical practice.¹ Less common, but by no means rare, is the severe form of erythema multiforme exudativum with predominant involvement of the mucous membranes.² Case reports describing the latter condition have appeared with increasing frequency in recent years. The earlier impression was that patients showing predominant involvement of the mucous membranes were severely ill but rarely died. It is now apparent that such illnesses vary widely in severity, from mild to fatal. Whether or not the symptom complex to be described is merely a severe type of the benign afebrile form of erythema multiforme exudativum, which involves the skin primarily, is unknown.

The present report deals with a description of 6 cases of erythema multiforme exudativum with predominant involvement of the mucous membranes of the mouth, seen at the Regional Station Hospital at Fort Bragg, N. C., during a period of three years. In 3 of the 6 cases, clinical and roentgenographic evidence of pulmonary involvement was

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1. Sutton, R. L., and Sutton, R. L., Jr.: *Diseases of the Skin*, ed. 10, St. Louis, C. V. Mosby Company, 1939.

2. Keil, H.: Erythema Multiforme Exudativum: A Clinical Entity Associated with Systemic Features, *Ann. Int. Med.* **14**:449-494, 1940.

demonstrated. On the basis of the clinical and laboratory findings it was believed that the pulmonary lesions were due to nonbacterial pneumonia. The pneumonia appeared to be an integral feature of the disease and could not readily be considered a secondary complication. The chief purpose of this report is to emphasize the relationship of pneumonia to erythema multiforme exudativum, since it is a feature which has not been stressed sufficiently in previous descriptions of this condition. That such a relationship exists, however, is evident from a review of the literature, which reveals numerous examples of the occurrence of pneumonia in cases of erythema multiforme exudativum.³

Whether erythema multiforme exudativum is an etiologic entity is unknown. It has been regarded as a specific infectious disease, possibly of virus causation.² Apart from bacteriologic studies, however, little serious effort has been made to isolate an infectious agent by the inoculation of laboratory animals. Such an attempt was made with the present cases, and the results of these studies will be presented in this report.

HISTORICAL REVIEW

Several excellent reviews have pointed out the unity and relationship of the cases reported by many authors under a confusing variety of labels.⁴ Unfortunately this knowledge is still not widely appreciated among internists, pediatricians, ophthalmologists, and dentists. All these specialists occasionally see cases in which there is predominant involvement of structures which bring the patient within the domain of their specialty. Accordingly a brief historical review is believed profitable.

In 1860 Hebra separated from the ill defined group of erythemas an entity which he called "erythema multiforme exudativum."⁵ He did not describe lesions of the mucous membrane. Bazin enlarged the clinical picture by describing cases in which vesiculobullous stomatitis was present as well as cutaneous lesions.⁶ He also noted the frequent

3. During the summer and fall of 1942, at the Boston City Hospital, Dr. Maxwell Finland studied several cases of erythema multiforme exudativum with pulmonary involvement. Some of us had the opportunity to see these cases. This experience stimulated our interest in the condition and aided in our subsequent recognition of similar cases at Fort Bragg.

4. (a) Keil.² (b) Klauder, J. V.: *Ectodermosis Erosiva Pluriorificialis: Its Resemblance to the Human Form of Foot and Mouth Disease and Its Relation to Erythema Exsudativum Multiforme*, Arch. Dermat. & Syph. **36**:1067-1077 (Nov.) 1937. (c) Lever, W. F.: *Severe Erythema Multiforme: Report of Two Cases of the Type Ectodermosis Erosiva Pluriorificialis, with Development of Cicatricial Conjunctivitis and Keratitis in One Case*, *ibid.* **49**:47-56 (Jan.) 1944.

5. Hebra, F.: *Diseases of the Skin*, translated and edited by C. H. Fagge, London, New Sydenham Society, 1866.

6. Bazin, E.: *Leçons théoriques et cliniques sur les affections génériques de la peau*, Paris, A. Delahaye, 1862; quoted by Keil.²

occurrence of fever and prodromal constitutional symptoms. In 1916 Rendu, and later others, described similar cases with fever, constitutional symptoms, and a vesiculobullous eruption involving lips, mouth, conjunctivas, glans penis and skin. They regarded this as a distinct entity, describing it as "erythema erosiva pluriorificialis."⁷ In 1922, Stevens and Johnson reported 2 cases of this syndrome in a severe form and believed it to be a hitherto undescribed entity.⁸ Subsequently the eponym "Stevens-Johnson" has been applied with increasing frequency in this country although it has no historical justification. Other descriptive labels used since then were "dermatostomatitis,"⁹ "ulceromembranous stomatitis,"¹⁰ and "mucocutaneous fever."¹¹

CLINICAL PICTURE

An excellent summary of the clinical features of this disease is to be found in the review of Keil.² This author championed the point of view which emphasizes the unity of the benign and severe forms of erythema multiforme exudativum as varying manifestations of a single clinical entity. Erythema multiforme exudativum is a disease of short course, usually benign, characterized by a cutaneous eruption with a predilection for certain parts of the body, involvement of the mucous membrane, constitutional symptoms, seasonal occurrence, predominant incidence in young adults and recurrent attacks. There is no sex difference in the incidence of the disease.

The cutaneous lesions are of two types: erythematopapular and vesiculobullous. Lesions are most frequent on the dorsa of the hands and the feet, and they spread up the extensor surfaces of the arms to the sides of the neck and face and up the legs and thighs; they may be numerous or rather sparse. Not infrequently the scrotum is involved, but lesions occur on the trunk less commonly except in some of the cases of severer disease. Erythematopapular lesions are characterized by peripheral extension with recurrent efflorescence at the centers, giving rise to erythema iris lesions and their variants. Vesiculobullous lesions usually arise from the preceding erythematopapular type when

7. Rendu, R.: Sur un syndrome caractérisé par l'inflammation simultanée de toutes les muqueuses externes (conjunctivale, nasale, linguale, bucco-pharyngée anale et balano-préputiale) coexistant avec une éruption varicelliforme puis purpurique des quatre membres, *Rev. gén. de clin. et de thérap.* **30**:351, 1916.

8. Stevens, A. M., and Johnson, F. C.: A New Eruptive Fever Associated with Stomatitis and Ophthalmia: Report of Two Cases in Children, *Am. J. Dis. Child.* **24**:526-533 (Dec.) 1922.

9. Baader, E.: Dermatostomatitis, *Arch. f. Dermat. u. Syph.* **149**:261-268, 1925.

10. Henry, T. C.: Ulcero-Membranous Stomatitis: Three Atypical Cases, *Brit. M. J.* **2**:273-276 (Sept. 5) 1942.

11. Haddad, N. N.: Muco-Cutaneous Fever, *J. Canad. M. Serv.* **2**:657-662, 1945.

the exudation of fluid is excessive. Both types of lesions are frequently present together. The bullous or vesicular lesion therefore is usually bordered by an erythematous halo. The vesiculobullous variety is more commonly associated with lesions of the mucous membrane and with fever and constitutional symptoms; hence it is more often seen by internists, pediatricians and ophthalmologists. Since the predominantly erythematopapular variety exhibits less, if any, fever or constitutional symptoms and less commonly involves the mucous membranes, it is more likely to be seen by the dermatologist or general practitioner.

Involvement of the mucous membrane is an integral feature of the disease. Its incidence has been estimated as approximately 25 per cent in all cases, and higher in the vesiculobullous variety.² In the latter cases, lesions of the mucous membrane may be the most prominent feature of the disease. Recurrent attacks in a single case may involve both skin and mucous membranes, skin only, or mucous membranes only.¹² As in the skin, lesions of the mouth begin with initial erythematous macules in which vesicles and bullae form. These quickly become eroded, leaving superficial ulcerations covered with white or grayish membranes bordered by zones of erythema. The lesions may be few and discrete, or confluent and involving the whole of the buccal, gingival and palatal mucosa and extending as well into the pharynx and below. Healing is eventually complete, without scarring, unless there is extensive secondary infection. This is likewise true in the skin.

Conjunctival involvement is common. Most often the inflammation is catarrhal and heals completely. In a number of cases it has been purulent or pseudomembranous, leading either to perforation of the cornea and panophthalmitis, necessitating enucleation, or to chronic infiltration of the conjunctivas and the cornea with scarring and adhesions.¹³ Severe involvement of the eyes, usually associated with lesions of the mouth but occasionally with little or no involvement of the skin, has been reported.¹⁴

12. (a) Edgar, K. J., and Syverton, J. T.: Erythema Exudativum Multiforme with Ophthalmia and Stomatitis: Report of Two Cases in Children with Certain Observations on Histopathology and Animal Inoculation, *J. Pediat.* **121**:151-159, 1938. (b) Butler, J.: Erythema Multiforme Confined to the Mucous Membranes with Report of Case, *Arch. Dermat. & Syph.* **6**:1-5 (July) 1922.

13. Ginandes, G. J.: Eruptive Fever with Stomatitis and Ophthalmia: Atypical Erythema Exudativum Multiforme (Stevens-Johnson), *Am. J. Dis. Child.* **49**:1148-1160 (May) 1935.

14. (a) Koke, M. P.: Conjunctivitis in Erythema Exudativum Multiforme: Report of Three Cases, *Arch. Ophth.* **25**:78-88 (Jan.) 1941. (b) Bailey, J. H.: Lesions of the Cornea and Conjunctiva in Erythema Exudativum Multiforme (Hebra): Report of Three Cases with Grave Ocular Sequelae, *ibid.* **6**:362-379 (Sept.) 1931. (c) Kove, S.: Stevens-Johnson Syndrome (Eruptive Fever with Stomatitis and Conjunctivitis), *Am. J. M. Sc.* **210**:611-623, 1945.

Other mucous membranes and mucocutaneous borders involved include the nares and the nasal mucosa, the lips, the urethral meatus, the glans penis, the anus, the vulva and the vagina. Involvement of the larynx, the trachea, the bronchi and the bronchioles and the occurrence of pneumonia will be discussed presently.

Systemic manifestations are commonly absent in the erythematopapular variety confined chiefly to the skin, but may be rather severe in cases of vesiculobullous disease, especially those predominantly involving the mouth and other mucous membranes. Rather commonly prodromal symptoms suggestive of respiratory infection, such as sore throat, cough, coryza, headache, malaise and feverishness, precede by a number of days the development of the enanthems. This feature was prominent in some of the cases to be presented. Fever appears to follow no particular pattern; the temperature may be only slightly above normal or as high as 105 F., and the temperature may remain abnormally high for one or more weeks, usually returning to normal before the healing of the lesions is well advanced. In the cases of severer disease lesions of the mouth appear either initially or after several days of prodromal fever and symptoms. Conjunctival, nasal and penile lesions generally follow, and, in time of appearance, cutaneous lesions often are the latest active manifestations of the disease.

The course of the disease is variable. New cutaneous lesions may continue to form for periods of one to four weeks. Lesions of the mucous membrane, particularly those in the eyes, may persist for months, although this appears to be unusual. Apart from pulmonary involvement, visceral lesions do not appear to be prominent, if they occur at all. Periarticular swelling has been described but not true articular effusions. Febrile albuminuria is common, but obvious involvement of kidneys, heart, liver or other organs is not known to occur. Lymphadenopathy is not prominent. There seems to be no consistent or characteristic change in the formed elements of the blood. Both leukopenia¹⁵ and leukocytosis¹⁶ have been reported, the latter more frequently; most cases, however, exhibit normal total and differential leukocyte counts throughout the illness. Usually eosinophilia does not occur.¹⁷ The few determinations of the chemical constituents of the blood that have been reported have yielded normal findings.¹⁸

15. (a) Stevens and Johnson.⁸ (b) Fletcher, M. W. C., and Harris, R. C.: Erythema Exudativum Multiforme (Hebra)-Bullous Type: Cases Seen in a Contagious Disease Hospital, *J. Pediat.* **27**:465-479, 1945.

16. (a) Haddad.¹¹ (b) Fletcher and Harris.^{15b} (c) Robertson, H. F., and Donovan, T. J.: Erythema Multiforme Exudativum or Bullosum, *Mil. Surgeon* **96**:259-262, 1945. (d) Rosenberg, L., and Rosenberg, J.: Erythema Exsudativum Multiforme (Hebra) with Conjunctivitis and Stomatitis, *Arch. Dermat. & Syph.* **41**:1066-1072 (June) 1940.

PATHOLOGY

There is a paucity of information regarding the pathology of erythema multiforme exudativum due to infrequent opportunity for histopathologic examination. In the vesiculobullous variety, the skin on microscopic section contained bullous lesions, some of them desquamated, leaving superficial ulcers limited sharply to the epidermis and the upper corium.¹⁹ Hanke²⁰ described intracytoplasmic inclusions in the conjunctiva; this observation awaits confirmation. The pathologic findings in the tracheo-bronchial tree and the lungs will be discussed subsequently. Other organs have shown only acute passive congestion.²¹

DIFFERENTIAL DIAGNOSIS

A number of diseases, at certain stages of their course, may exhibit pleomorphic erythematous eruptions, i. e. rheumatic fever, erythema nodosum, disseminated lupus erythematosus and bacteremia due to meningococcus and gonococcus organisms. Relatively few conditions, however, simulate the form of erythema multiforme exudativum characterized by vesiculobullous lesions of the skin and the mucous membranes. Among such diseases it is of importance to differentiate pemphigus. The distinction may be difficult, at times, but the age distribution of pemphigus, the development of bullae on apparently normal skin, positive Nikolsky sign, absence of fever in early stages, and particularly chronicity, are features of differential value, although in individual instances cases of erythema multiforme exudativum also exhibit these features. At times, chickenpox and generalized vaccinia have been confused with this condition.^{15b}

As a result of idiosyncrasy or hypersensitivity to a variety of drugs, a clinical condition of the skin and mucous membranes closely resembling, if not identical with, erythema multiforme exudativum may result.

17. Murphy, R. C.: An Eruptive Fever Involving the Mouth and Eyes (Stevens-Johnson's Disease): Report of a Case, *New England J. Med.* **230**:69-71, 1944.

18. (a) Fletcher and Harris.^{15b} (b) Smith, C. A.: Unusual Case of Erythema Multiforme, *Tr. Univ. Mich. Pediat. & Infect. Dis. Soc.*, 1929, pp. 63-67.

19. Edgar and Syverton.^{12a} Fletcher and Harris.^{15b}

20. Hanke, V.: Der Herpes iris des Auges, *Arch. f. Ophth.* **52**:263-284, 1901.

21. (a) Fletcher and Harris.^{15b} (b) Smith.^{18b} (c) Hanke.²⁰ (d) Welander, E.: Ein Fall von Erythema multiforme exsudativum mit tödlichem Ausgang, *Arch. f. Dermat. u. Syph.* **77**:289-296, 1905. (e) Corlett, W. T.: Erythema Exudativum Multiforme: Its Present Significance, with Report of a Case of Erythema Circinatum Bullosum et Haemorrhagicum, Following a Gunshot Wound, Apparently Due to Streptococcus Infection and Terminating Fatally, *J. Cutan. Dis.* **26**:7-14, 1908.

Among the drugs known to produce such reactions are phenobarbital,²² phenylethylhydantoin (nirvanol),²² diphenylhydantoin sodium,²³ phenolphthalein,²⁴ sulfathiazole²⁵ and sulfadiazine.²⁶ A careful history of medication preceding illness is essential in differential diagnosis. Sulfonamide compounds may be administered during the prodromal stages of erythema multiforme exudativum and thus be held responsible for the subsequent eruption.^{4c} In 1 of the cases in the present series (case 5) sulfadiazine was administered for four days and discontinued the day before the stomatitis appeared.

The clinical resemblance between erythema multiforme and the human form of foot and mouth disease has been pointed out.^{4b} Unfortunately, knowledge of the human manifestations of the latter disease is scanty. Toward the close of the nineteenth century large numbers of cases of this disease among human beings were reported, particularly in Continental Europe. Since modern knowledge of the virus causation of the disease became available²⁷ there have been few authentic reports of the occurrence of cases among human beings.²⁸ The course of these acceptable cases was short in duration and characterized by little or no fever and the appearance of vesicles in the mouth, on the lips and on the hands, particularly about the finger tips.^{28b} Thus, the authenticity of cases in which there were generalized eruptions, a high temperature, long duration and extensive involvement of the conjunctivas, the pharynx, the urethra and the anus is open to serious question.²⁹

Among diseases producing stomatitis which may be confused with erythema multiforme exudativum may be mentioned herpetic gingi-

22. Ellis, F. A.: Reactions to Nirvanol, Phenytoin Sodium, and Phenobarbital: Report of a Case of Ectodermosis Erosiva Pluriorificialis Following the Ingestion of Phenytoin Sodium, *South. M. J.* **36**:575-579, 1943.

23. Ellis,²² Ritchie, E. B., and Kolb, W.: Reaction to Sodium Diphenyl Hydantoinate (Dilantin Sodium): Hemorrhagic Erythema Multiforme Terminating Fatally, *Arch. Dermat. & Syph.* **46**:856-859 (Dec.) 1942.

24. Newman, B. A.: Phenolphthalein Intoxication, *J. A. M. A.* **101**:761-764 (Sept. 2) 1933.

25. Franks, A. G., and Traub, E. F.: Varioliform Eruption from Sulfathiazole, *Arch. Dermat. & Syph.* **46**:737-738 (Nov.) 1942.

26. Raffetto, J. F., and Nichols, S.: A Nearly Fatal Reaction to Sulfadiazine in a Ten Year Old Girl, Involving Skin, Eyes and Oropharynx, *J. Pediat.* **20**:753-755, 1942. Greenberg, S. I., and Messer, A. L.: Fatal Bullous Dermatitis Following Administration of Sulfadiazine, *J. A. M. A.* **122**:944 (July 31) 1943.

27. Waldmann, O., and Jape, J.: Die künstliche Uebertragung der Maul- und Klauenseuche auf das Meerschweinchen, *Berl. tierärztl. Wchnschr.* **36**:519, 1920.

28. Dlugosz, H.: Foot-and-Mouth Disease in Man, *Brit. M. J.* **1**:189-190, 1943. (b) Bojlén, K.: Foot-and-Mouth Disease in Man, *Ugesk. f. laeger* **103**:497-506, 1941.

29. Bojlén,^{28b} Arkwright, J. A.: Foot-and-Mouth Disease in Man, *Lancet* **1**:1191, 1928.

vostomatitis and Vincent's stomatitis. Neither of these conditions is associated with a generalized eruption of the skin and the mucous membrane. Primary herpetic stomatitis is a disease chiefly affecting young children and characterized by fever, irritability, oral fetor, soreness of the mouth and regional lymphadenopathy. The lesions are situated chiefly in the gums, which are red and swollen and bleed easily.³⁰ Lesions may involve any part of the oral mucosa and, in some cases, the tonsils and pharynx.³¹ Early in the course of the disease small pinhead size vesicles may be seen; these soon rupture, leaving round or irregular ovoid superficial ulcers. Herpes virus can be recovered readily by appropriate laboratory tests.³⁰

Vincent's infection is not characterized by an initial vesicular stage. Cases of typical erythema multiforme exudativum have been reported as oral Vincent's infections associated with erythema multiforme of the skin and the eyes; in such instances the description of the oral lesions was not characteristic of Vincent's disease, and the diagnosis rested merely on the presence of fusospirochetal organisms in smears.³²

MORTALITY

Erythema multiforme exudativum was originally described as a benign disease. The ordinary erythematous variety is rarely, if ever, fatal. The vesiculobullous type, and particularly those cases in which there is primary involvement of the mucous membrane, may be extremely severe. Although Lever^{4c} was able to find only 4 fatal cases in the literature, it is believed that fatalities are commoner than their reported incidence.

Markham,³³ in describing a fatal case of "atypical virus pneumonia" on which were superimposed a severe conjunctivitis, membranous stomatitis, bullous cutaneous eruption and balanitis, stated that of 5 similar cases, 4 were fatal. The occurrence of 5 cases of erythema multiforme bullosum in a total of 28 cases observed over a thirteen year period has also been reported.^{15b}

30. Dodd, K.; Buddingh, J., and Johnston, L.: Herpetic Stomatitis, *Am. J. Dis. Child.* **58**:907 (Oct.) 1939. Scott, T. F. M.; Steigman, A. J., and Convey, J. H.: Acute Infectious Gingivostomatitis, *J. A. M. A.* **117**:999-1005 (Sept. 20) 1941. Ziskin, D. E., and Holden, M.: Acute Herpetic Gingivostomatitis: Report of Fifteen Cases, *J. Am. Dent. A.* **30**:1697-1705, 1943.

31. Long, P. H.: Herpetic Pharyngitis and Stomatitis: Report of Three Cases, *J. Clin. Investigation* **12**:1119-1125, 1933.

32. Chick, F. E., and Witzberger, C. M.: Erythema Multiforme Exsudativum Accompanying Oral Vincent's Infection, *Am. J. Dis. Child.* **55**:573-578 (March) 1938. Morrison, J. P.: A Case of Vincent's Infection Associated with Erythema Multiforme, *J. Am. Dent. A.* **28**:1938-1940, 1941.

33. Markham, J. D., in the Clinical Meeting of the Kingston Garrison Medical Society, *J. Canad. M. Serv.* **1**:471, 1944.

CAUSATION

The cause of the disease is unknown. The results of bacteriologic studies were inconclusive. Blood cultures have uniformly failed to yield bacterial growth.³⁴ Cultures of the involved eyes have either been sterile or yielded growth of normal flora, such as *Staphylococcus albus* or *Streptococcus viridans*.^{15b} Streptococci have been recovered rather frequently from cultures from the mouth and throat, and some authors have been impressed by the possible causal significance of this finding.¹⁰ It is apparent, however, that the organisms isolated were not always beta hemolytic streptococci.¹⁰ Kove^{14c} found hemolytic streptococci in throat cultures from both of his cases. However, in another series, these organisms were recovered from throat cultures in only 3 of 14 cases.^{15b} Moreover, in another case beta hemolytic streptococci were present in the throat during the first attack of the disease but were not found in a recurrence six months later.¹²ⁿ In 1 fatal case streptococci may have played a role, since they were recovered in pure culture from bullae.^{21e} In contrast, most of the bullae cultured by other observers have been sterile.³⁵ It is apparent, therefore, that hemolytic streptococci are not found with enough consistency in the majority of cases to suggest their causal relationship to the disease. In occasional instances, they may play a contributory or secondary role. Case 3 of the present series is an example of this. Aside from the streptococcus no organism has been incriminated as a causative agent of the disease. Fusospirochetal organisms have been present in some cases³² and absent in others.³⁶

Only two reports were encountered in which inoculations in animals were undertaken. Vesicular fluid from 1 patient was inoculated in mice, rabbits and guinea pigs; in each instance the intracerebral, intraperitoneal and intradermal (foot pad) route was used.^{12a} In another case, guinea pigs were inoculated in the foot pads with vesicular fluid.^{14a} The negative results obtained in both of these studies offered presumptive evidence excluding the presence of the viruses of herpes simplex and foot and mouth disease.

The following cases were observed on the medical wards of the Regional Station Hospital at Fort Bragg, N. C. The management of the cases was determined by the medical officers in charge.

REPORT OF CASES

CASE 1 (fig. 1).—An 18 year old white soldier with two months of Army service was hospitalized on May 5, 1943, complaining of photophobia and itching of the eyes, sore mouth and throat and cough.

34. Fletcher and Harris.^{15b} Murphy.¹⁷

35. Kove.^{14c} Fletcher and Harris.^{15b} Murphy.¹⁷

36. Edgar and Syverton.^{12a} Kove.^{14c} Rosenberg and Rosenberg.^{16a}

The illness began on April 28 with malaise, which improved the next day. On April 30 he awoke with a cough which was at first dry; after a few days it became moderately productive and was associated with headache. The day before hospitalization his eyes began to itch, and photophobia developed. The next day the mouth and the throat became sore. No history of ingestion of drugs could be elicited. Of possible significance was a history of "trench mouth" several years previously.

At the time of admission the patient appeared moderately ill and extremely uncomfortable. The buccal mucosa and the pharyngeal walls were coated with thin white "slimy" exudate. On the hard palate were a few whitish irregular patches, each somewhat less than 1 cm. in diameter. The lips were swollen, and on the lower lip were several small vesicles. The patient could scarcely open his eyes because of photophobia, and yellowish exudate appeared between the closed lids. Both the palpebral and the bulbar conjunctivas were edematous and diffusely

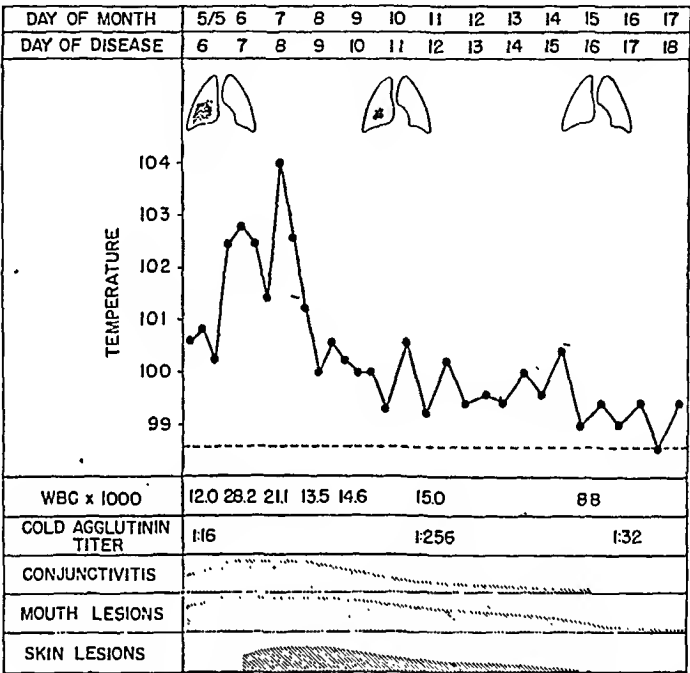


Fig. 1 (case 1).—Erythema multiforme exudativum and pneumonia.

injected. The submaxillary lymph nodes were enlarged and tender. At the base of the right lung posteriorly moderate dullness and numerous fine rales were elicited. The remainder of the physical examination revealed no abnormality.

The temperature rose to a maximum of 104 F. on the third hospital day, and thereafter low grade fever persisted for a week. The course was one of progressive involvement of the mucous membranes of the lips, the mouth, the pharynx and the eyes for four days followed by slow healing of the lesions. At the height of the reaction the buccal and pharyngeal mucosa, the tongue and the nasal mucosa were covered with a "slimy" white pseudomembrane, which was not unusually foul smelling. Successive crops of vesicles appeared on the lips, and in a few hours they became macerated and took on the appearance of the whitish patches in the mouth.

On the day after the patient's admission crops of deep-seated, "shotty" grayish vesicles, surrounded by an erythematous halo, appeared on the palms; they persisted for more than a week. No other areas of the skin were involved.

By the tenth day of disease involution of all lesions was evident, and the subjective complaints referable to the eyes and the mouth lessened. Rales in the right lung were audible until the twentieth day of illness. The total duration of hospitalization was six weeks, but eventual full restoration to normal health resulted. Treatment was palliative and symptomatic, consisting of sedatives, hydrogen peroxide and sodium perborate mouth washes; later sulfathiazole pastes, and boric compresses to the eyes were used.

Pertinent laboratory data are indicated in figure 1. The roentgenogram of the chest taken on admission showed rather extensive nonlobar infiltration, of a feathery character, in the lower lobe of the right lung which resolved and disappeared in the course of two weeks (fig. 2). Despite the leukocytosis during the febrile period, the differential formula was normal except for 8 per cent eosinophils at the time of admission. In subsequent differential counts the eosinophils were not above 4 per cent. Numerous analyses showed the urine to be

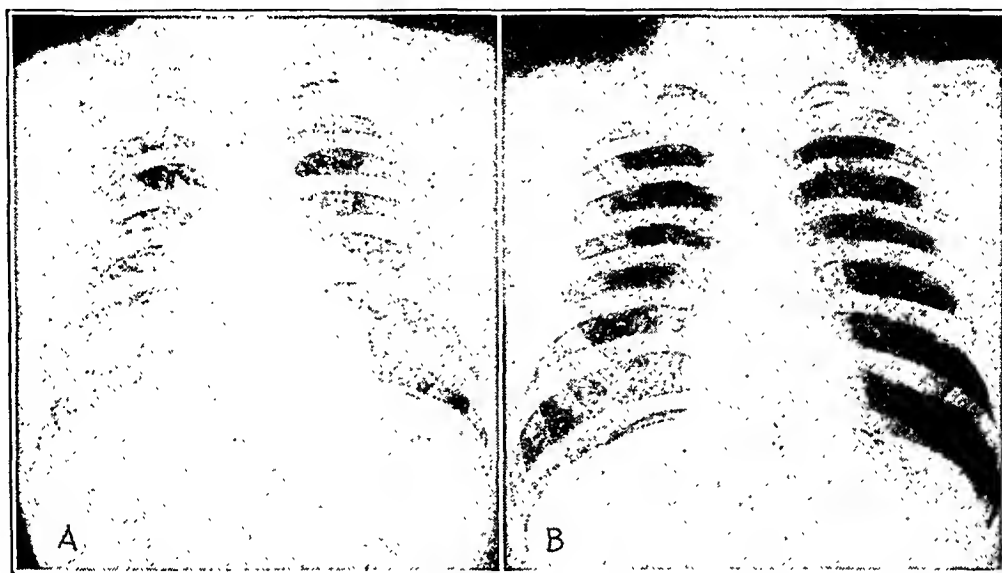


Fig. 2 (case 1).—*A*, sixth day of illness; pneumonic infiltration, lower lobe of right lung. *B*, twenty-second day of illness; lung fields clear.

normal except for slight albuminuria. The Kahn reaction was reported as doubtfully positive on the ninth day of illness and negative on the twelfth day.

Numerous cultures of material taken from the mouth and the pharynx at intervals during the course of the illness and incubated aerobically showed only a few colonies of *Hemophilus influenzae* and *Hemophilus haemolyticus*. Conjunctival cultures were sterile. A blood culture obtained at the height of fever was sterile. Cold hemagglutinins developed in maximum titer of 1 to 256 on the twelfth day of illness.³⁷ Antistreptolysin titers on acute and convalescent phase serums gave no indication of hemolytic streptococcus infection.

CASE 2 (fig. 3).—A 22 year old white soldier with two months of service was admitted to the hospital on Dec. 5, 1942, complaining of sore throat.

37. Commission on Acute Respiratory Diseases: Cold Hemagglutinins in Primary Atypical Pneumonia and Other Respiratory Infections, *Am. J. M. Sc.* **208**: 742-750, 1944.

The illness began on December 2 with sore throat, cough, malaise, chilliness and feverishness. There was no history of recent ingestion of drugs, and the past history seemed irrelevant.

At the time of admission the patient appeared to be only mildly ill. The only abnormal physical finding was a moderate degree of pharyngeal injection, and an initial diagnosis of "nasopharyngitis" was made.

During the first four hospital days the patient made no complaints, but had a low grade fever, with a temperature which was not above 100.6 F. On December 9 he began to complain of a sore mouth, accounted for by the finding of several bullae on the floor of the mouth under the tongue. The cervical lymph nodes were not enlarged or tender. At this time the temperature rose to 102 F., and although the lungs were clear on physical examination a roentgenogram showed a moderate amount of soft infiltration in the lower lobes of both right and left lungs. For the next five days the temperature was persistently elevated

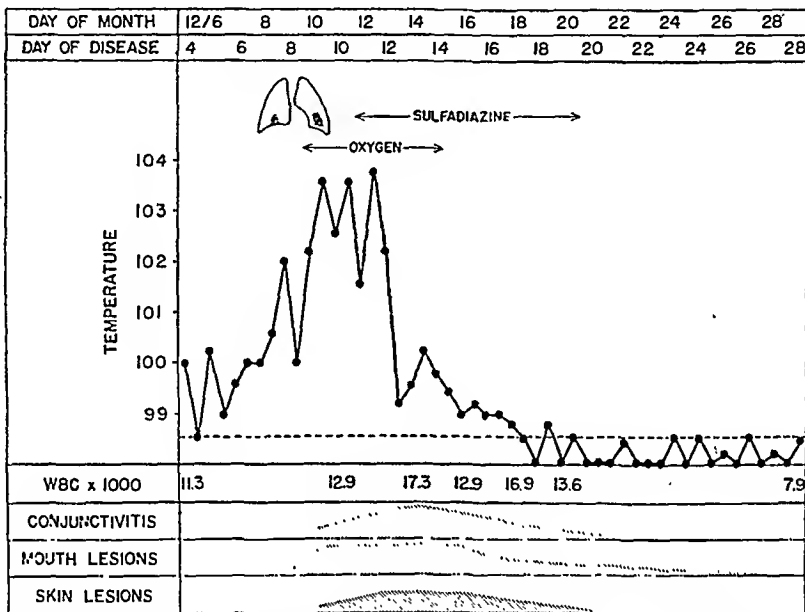


Fig. 3 (case 2).—Erythema multiforme exudativum and pneumonia.

between 102 and 104 F. The patient became somewhat dyspneic and slightly cyanotic on the lips and nail beds and was placed in an oxygen tent. Rales over both lung bases and moderate dullness over the base of the right lung posteriorly were first detected on December 12. The lesions in the mouth, first noted on December 9, spread rapidly, and the buccal and gingival mucosa, the soft palate and the pharynx were covered with a patchy, grayish membrane, and the mucosa itself became fiery red. Despite the extensiveness of the exudate it was not especially malodorous. On December 10 the conjunctivas of both eyes became diffusely injected. On the same day the patient complained of dysuria, and an excoriated area covered with seropurulent exudate was seen at the tip of the urethral meatus. For a week the patient was miserable because of profuse salivation, extreme difficulty in swallowing and speaking, cough and dysuria, but by the sixteenth day of illness the oral and penile lesions had begun to heal, the temperature was nearly normal and the respiratory distress had disappeared. Convalescence proceeded uneventfully, and complete recovery followed.

Treatment was symptomatic except for the administration of sulfadiazine from December 12 to December 20. The temperature fell toward normal shortly after chemotherapy was begun, but it is not clear whether this result was coincidental or due to therapy.

Slight leukocytosis with normal differential leukocyte counts was found during the first week of illness. At the end of the febrile period there was more definite elevation of the total leukocyte count associated with an increase in polymorphonuclear leukocytes to 87 per cent. The urine was normal throughout the illness. Stained smears from the mouth and the throat revealed only a small number of fusiform bacilli and spirochetes. Aerobic cultures of the throat and the sputum revealed only normal flora. Staphylococcus albus was cultured from the urethral lesion. A blood culture obtained at the height of fever on December 11 was

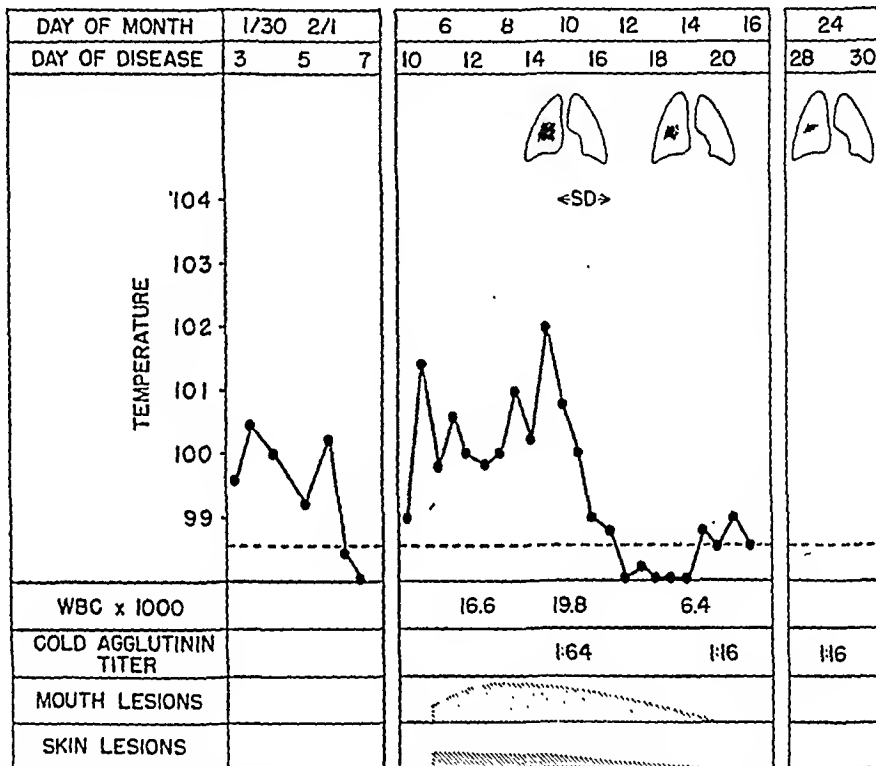


Fig. 4 (case 3).—Erythema multiforme exudativum and pneumonia; concurrent hemolytic streptococcus infection.

sterile. Specimens of serum were not obtained, so that cold hemagglutinin and other serologic tests could not be performed.

CASE 3 (fig. 4).—A 23 year old white soldier with a year and a half of military service was admitted to the hospital on Jan. 29, 1944, complaining of feverishness, sore throat, cough and substernal pain of two days' duration. He did not appear seriously ill. The only abnormal finding was moderate injection of the pharynx, without exudate; the remainder of the physical examination, including that of the chest, revealed no abnormality. The temperature on admission was 100.4 F., falling to normal on the fourth hospital day. With bed rest the symptoms subsided, and the patient was discharged to duty on February 2, with a diagnosis of "common cold." No laboratory studies were made. While in the hospital he received codeine and acetylsalicylic acid; there was no history of preceding medication.

On February 5 the patient was readmitted to the hospital because of a recrudescence of sore throat. Physical examination again yielded normal findings except for an injected pharynx and moderately enlarged and tender cervical lymph nodes. The next day the patient complained for the first time of soreness in the mouth and, later on the same day, of dysuria. The mucous membranes of the mouth at this time were found to be diffusely reddened with patches of whitish exudate on the buccal mucosa, the gums, the soft palate and the pharynx. At the urethral meatus was a red excoriated lesion resembling the base of a vesicle from which the top had been removed. No other cutaneous lesions appeared, nor were the conjunctivas or nasal mucosa involved. On February 10 rales were heard at the base of the right lung posteriorly. Although the patient was uncomfortable because of the soreness of the mouth, at no time did he appear acutely or seriously ill. The oral and penile lesions healed by February 14, but the cough and the abnormal physical signs in the chest persisted for another week.

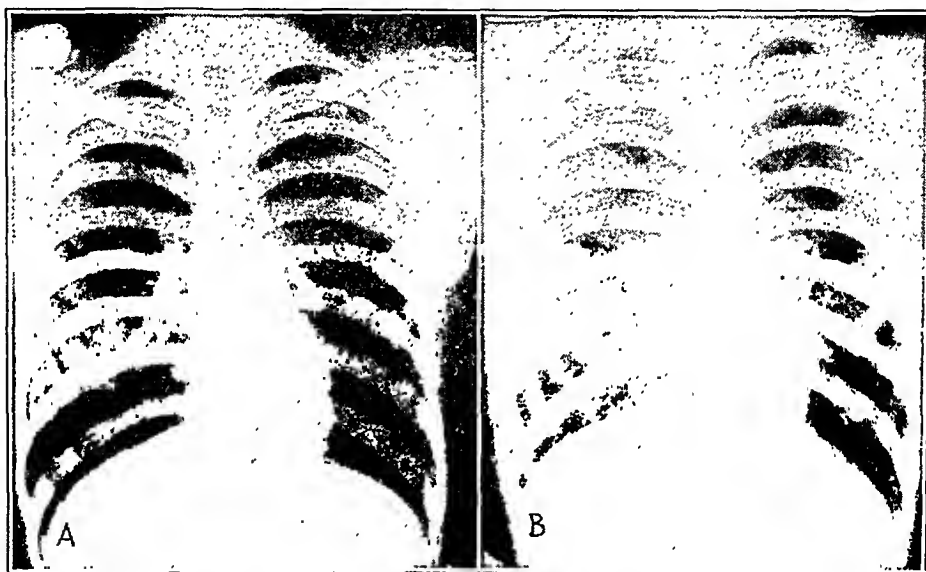


Fig. 5 (case 3).—*A*, fifteenth day of illness; pneumonic infiltration, right mid-lung field. *B*, thirty-fourth day of illness; lung fields clear.

Treatment was symptomatic except for the use of sulfadiazine on one day. Acetylsalicylic acid and codeine were administered throughout the hospital stay.

Roentgenograms of the chest on February 10 showed soft peribronchial infiltration in the middle lobe of the right lung (fig. 5). This lesion resolved slowly and was no longer visible in roentgenograms on February 29. The patient exhibited leukocytosis, as indicated in figure 4, but the differential leukocyte counts were normal. The urine was normal.

Cultures of material obtained from the throat on February 6, 10 and 16 and a culture of the sputum on February 19 all showed a small number of colonies of beta hemolytic streptococci of group A, type 30, without other significant bacterial organisms. Examination of smears of the mouth and the throat revealed no fusiform bacilli or spirochetes. A urethral smear showed gram-negative bacilli.

In addition to the elevated titer of cold hemagglutinins shown in figure 4, a diagnostic increase in antistreptolysin titer of 5 dilution increments was demonstrated in convalescent phase serums.

CASE 4 (fig. 6).—A 36 year old white soldier with two years of military service was admitted to the hospital on April 2, 1944, complaining of sore throat and hoarseness.

The patient was well until March 30, when he noted cough and slight pain on swallowing, both symptoms increasing in severity until admission. He denied feeling feverish or chilly but noted that his eyes were dry and irritated. There was no history of recent ingestion of drugs. Of possible significance was the patient's military occupation, which was that of butcher; his principal duty was the handling of frozen meats.

On admission the patient appeared acutely ill and in great distress because of difficulty in speaking and swallowing. The lips, the buccal mucosa, the tongue, the soft palate and the uvula, the tonsils and the pharyngeal walls were uniformly covered by a rather thick, gray-green, foul-smelling membrane. The mucosa

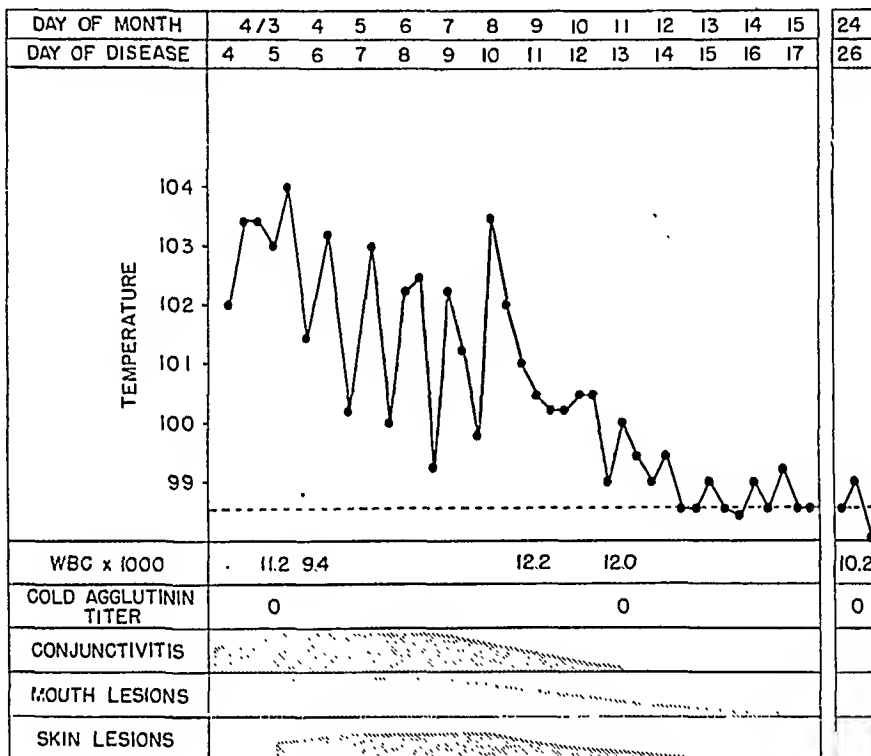


Fig. 6 (case 4).—Severe erythema multiforme exudativum without pneumonia.

underneath was deep red. The bulbar and palpebral conjunctivas were intensely red, edematous and covered with purulent exudate. There were several small conjunctival hemorrhages. On the palms and the backs of the hands and on the soles were numerous rather deep-seated unilocular firm vesicles, about 0.5 cm. in diameter, and surrounded by a narrow erythematous zone. On the under surface of the scrotum and about the meatus of the glans penis were a number of weeping excoriated lesions having the appearance of broken vesicles. The skin was elsewhere uninvolved. The lungs were clear. There was no cervical or generalized lymphadenopathy, and the remainder of the physical examination revealed no abnormality.

For a week the patient was acutely ill. He was unable to speak and could swallow only with great difficulty. It was necessary to administer fluids parenterally during this time. The temperature was irregular and swinging, varying between 99.2 and 104 F. for eight days. By the twelfth hospital day definite

improvement in the condition of the mouth and the eyes was evident, and the cutaneous lesions began to dry up. A few macular lesions subsequently appeared on the extensor surfaces of the elbows and on the soles. On a few occasions fine and coarse rales were heard in the chest. Recovery was slow but eventually complete.

Therapy was symptomatic and consisted of compresses and ointments to the eyes and cutaneous lesions and saline and sodium perborate mouth washes.

Roentgenograms of the chest on the fifth and eighth days of illness were normal. The serologic test for syphilis (Kahn) elicited a negative reaction. The total leukocyte counts were not remarkable (fig. 6), and the differential counts were normal. The urine was normal except for transient febrile albuminuria. Cultures of the conjunctivas yielded no bacterial growth. Throat cultures revealed only normal flora. Cold hemagglutinins were not present in the patient's serums, and there was no change in antistreptolysin titer during and after the illness.

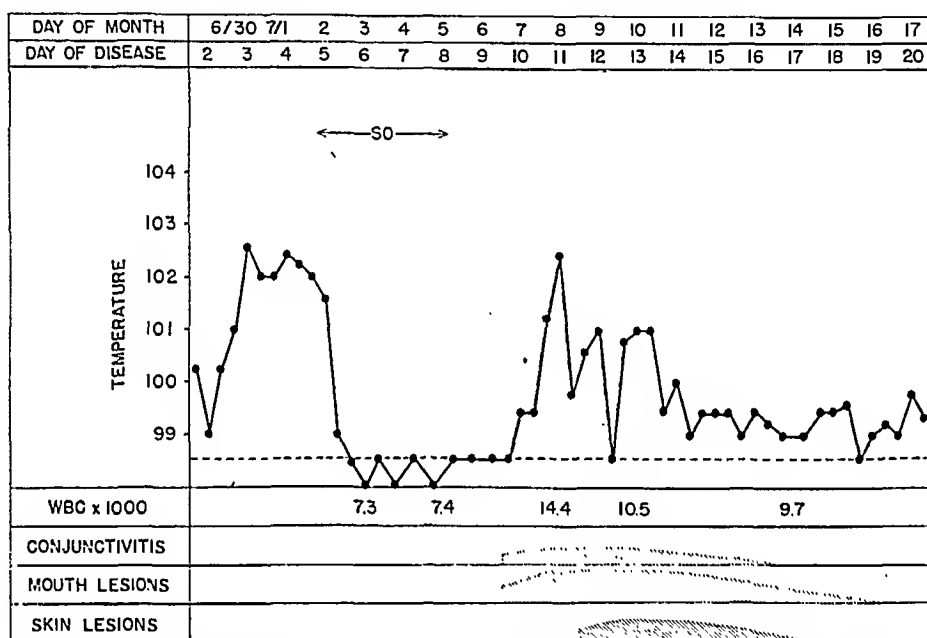


Fig. 7 (case 5).—Erythema multiforme exudativum without pneumonia.

Histologic section of a biopsy specimen taken from the margin of one of the cutaneous lesions showed no inclusion bodies and only nonspecific inflammatory changes.

CASE 5 (fig. 7).—An 18 year old white soldier with one month of military service was admitted to the hospital on June 29, 1943, complaining of sore throat. The patient was undergoing dental treatment for carious teeth, and on June 19 and 26 several teeth were extracted. On the day before hospitalization a sore throat developed, but he had no other symptoms. The past history was noncontributory. A history of recent medication was not obtained.

At the time of admission the temperature was 100.2 F., and the patient appeared only mildly ill. The only abnormal findings were moderate redness of the pharynx and many carious teeth. The day after admission the temperature rose to 102.4 F., and it remained at this level for three days. During this time there were no further abnormalities observed, although the patient still complained

of sore throat. Because of the fever, sulfadiazine was administered from July 2 to July 5, in a total dose of 18 Gm., during which time the temperature returned to normal.

On July 6 the patient first complained of a sore mouth. The next day numerous bullae, containing clear fluid, were seen on the inner borders of the lips and on the buccal mucosa. On the gums and the under surface of the tongue were whitish plaques of necrotic tissue and exudate, not easily removed, and appearing to be the remains of macerated bullae. In a few areas the mucous membrane was excoriated. Lesions were present also on the tonsils, the pharyngeal wall and the tip of the uvula. There was no cervical lymphadenopathy. The conjunctivas were injected but contained no exudate.

In the course of the next three days new bullae continued to appear, and the condition of the mouth grew worse. Confluent thin grayish white membranes covered most of the buccal, gingival and palatal mucosa. Swallowing became difficult and painful. On July 9 several maculopapular lesions, somewhat viola-

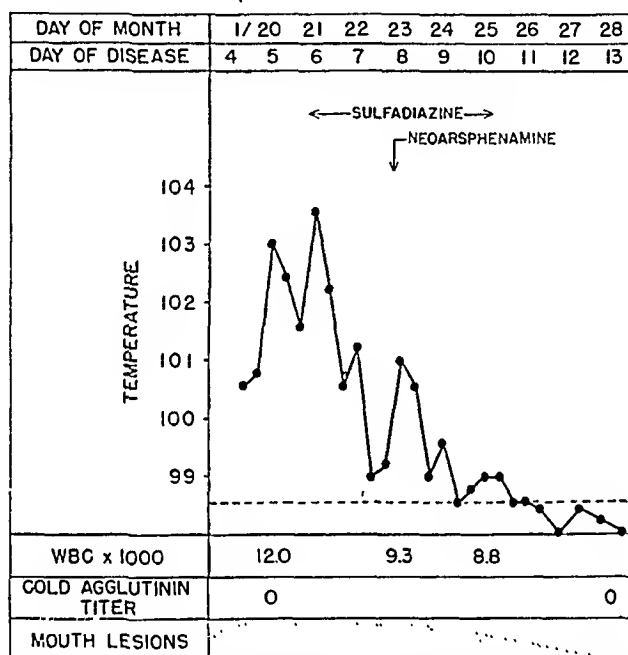


Fig. 8 (case 6).—Erythema multiforme exudativum confined to the mucous membranes of the mouth.

aceous, were found grouped about the urethral meatus; they soon became ulcerated and crusted. During this time there was a second febrile period lasting four days. By July 14 improvement in the condition of the mouth was evident, and at this time the penile lesions were healed and the conjunctivitis had subsided. The lesions in the mouth were treated with saline gargles, hydrogen peroxide and gentian violet medicinal. The patient was returned to duty on July 24, fully recovered.

A series of roentgenograms of the chest taken on June 29 and July 2, 7 and 12 all were normal. Total and differential leukocyte counts were normal throughout the illness except for one observation during the second febrile period. The urine was normal. Cultures of material from the throat revealed only normal flora. Serologic studies were not made.

CASE 6 (fig. 8).—A 22 year old white soldier with one year of military service was admitted to the hospital on Jan. 19, 1943, because of a sore throat. Nine

days before admission he complained of feverishness, chilliness, malaise, cough and sore throat and was confined to quarters for several days. These symptoms subsided, and he returned to duty. Three days before admission hoarseness developed, his mouth became sore, and swallowing became painful.

The patient was only mildly ill but extremely uncomfortable because of the condition of his mouth, which showed a pronounced generalized stomatitis and gingivitis with numerous vesicular lesions on the buccal and palatal mucosa, some of which were hemorrhagic. In addition there were many plaques of grayish exudate on the gums, the angles of the lips and the buccal and palatal mucosa. The posterior pharynx was not severely involved, and indirect visualization revealed only redness of the supraglottic structures and the vocal cords. The cervical lymph nodes were enlarged but not tender. There were no conjunctival or cutaneous lesions. The lungs were clear, and the remainder of the physical examination revealed no abnormality.

The maximum temperature was 103.6 F., and a temperature of 100 F. or more persisted for five days in the hospital. The oral lesions improved slowly over the course of ten days. Sulfadiazine, neoarsphenamine and local applications of sodium perborate were used in treatment, without obvious effect.

Roentgenograms of the chest on January 20 and 25 were normal. The leukocyte count was moderately elevated on admission but normal thereafter, and the differential leukocyte counts were normal throughout. The Kahn reaction was negative. Urinalysis yielded only normal findings. Three aerobic cultures of material from the mouth and throat revealed only normal flora (*alpha streptococci*, *Hemophilus influenzae*, and *Staphylococcus aureus*). On one stained smear of the oral lesions "many" fusiform bacilli were seen; on another, no fusiform bacilli or spirochetes. A blood culture remained sterile.

ETIOLOGIC STUDIES

An attempt was made to transmit an infectious agent to various animal species using blood, throat washings, vesicle fluid and other materials obtained from some of the patients included in this report. Although these studies were extensive in nature, employing a variety of animals as well as embryonated hens' eggs, the results were negative. Nevertheless, because there have been so few reported studies of this kind in cases of erythema multiforme exudativum it is believed worth while to describe the procedures in some detail.

Material from 4 of the cases was available for inoculation in animals and eggs. In addition, lung from a fatal case, obtained in the frozen state, was tested for infectivity.³⁸

In each instance material for inoculation was obtained at the height of the disease. The procedures were carried out immediately after the

38. The patient died three days after admission to the hospital, exhibiting signs of pneumonia and widespread vesicular lesions of the skin and the mucous membrane, typical of the severe form of erythema multiforme exudativum. Portions of lung were sent to this laboratory through the action of Major C. T. Nelson, Medical Corps, Army of the United States, of the Fourth Service Command Laboratory and Lieut. Col. T. C. Goodwin, Medical Corps, Army of the United States, and Capt. Parker Beamer, Medical Corps, Army of the United States, the Station Hospital, Fort McPherson, Ga.

Summary of Attempts to Isolate an Agent in Animals and Eggs from Cases of Erythema Multiforme Exudativum *

Case No.	Material	Animal		Initial Passage		Subsequent Passages					Histologic Sections Examined	
		Number		Route	Observation, Days	Number	Animals per Passage, No.	Inter-Passage, Days	Inoculum	Route		
1	Vesicular fluid	Unfiltered	Mice.....	2	I.c.....	13	2	3	10	Brain	I.n.	Yes
	Exudate, eyes	Unfiltered	Mice.....	6	I.c.....	13	2	3	10	Lung	I.n.	
	Exudate, palate	Unfiltered	Mice.....	3	I.p.....	20	3	3	10	Brain	I.n.	
	Sputum	Unfiltered	Mice.....	6	I.n.....	10	2	3	9	Liver and spleen	I.n.	
				6	I.n.....	20	3	3	10	Lung	I.n.	
				4	I.p.....	20	3	3	10	Liver and spleen	I.n.	
	Blood, defibrinated	Unfiltered	Mice.....	4			2	3	10	Liver and spleen	I.n.	
	Throat washings	Unfiltered and filtered	Rabbit.....	1	Cornea.....	5	2	3	10	Lung	I.n.	
			1	Eye, ant. chamber.....	23	2	3	10				
			2	I.c.....	23	2	3	10				
	Vesicular fluid and blood, defibrinated	Unfiltered	Guinea pig.....	2	I.d. and foot pad.....	23	1	15	1-4	CHA	CHA	Yes
	Vesicular fluid	Filtered †	Egg.....	6	CHA.....	1-4	1	1	3	Cornea	Cornea	
		Unfiltered	Egg.....	12	CHA.....	1-4	1	1	10	Skin of penis	Penis	
		Unfiltered	Rabbit.....	1	Cornea.....	3	1	1	10			
		Unfiltered	Monkey, rhesus.....	1	Penis, cornea, i.d.....	21	1	1	10			
		Unfiltered †	Rabbit.....	1	I.d., penis.....	21	2	4-8	4	Embryo and amniotic fluid	Amniotic	
			Egg.....	3	Amniotic.....	3	2	4-8	4			
			3	I.c.....	3		1	4	4	Brain	I.c.	
			1	Eye.....	3-4		1	4	4	Eye	Eye	
			6	I.d. and penis.....	4		3	6-8	4			
5	Blood, defibrinated	Unfiltered	Rabbit.....	1	I.c.....	21	2	4-8	4	CHA	CHA	Yes
		Filtered †	Mice.....	4	I.c.....	21	2	4-8	3	Amniotic fluid	Amniotic	
			Hamster.....	4	I.c.....	21	1	4	3	Brain	I.c.	
			Cotton rat.....	4	I.c.....	21	2	4-8	4			
			Egg.....	3	I.c.....	21	2	4-8	3			
			3	CHA.....	3		2	4-8	4	CHA	CHA	
			3	Amniotic.....	4		2	4-8	3	Amniotic fluid	Amniotic	
			3	I.c.....	4		1	4	3	Brain	I.c.	
			3	Eye.....	4		2	4-8	4			
			10	Cornea.....	21		2	4-8	3			
6	Vesicular fluid	Unfiltered	Rabbit.....	2	I.c.....	21	3	6-8	4			Yes
			Mice.....	10	I.c.....	21	2	4-8	3			
			8	I.n.....	21	2	4-8	3				
			2	I.n.....	7-28	3	4-6	7-10	Lung	I.n.		
			6	I.c.....	7	1	4	3	Brain	I.c.		
			6	I.c.....	3-28	2	4-6	7-10				
			1	Cornea.....	7	3	4-6	7-10				
			1	I.d. and penis.....	14	1	4	3				
			1	I.c.....	14	2	4-6	7-10				
			2	I.d. and foot pad.....	14	3	6-7	3	CHA	CHA		
Fatal Lung Case		Unfiltered	Monkey, rhesus.....	3	I.d. and penis.....	14	3	6-7	3	Amniotic fluid	Amniotic	Yes
			Mice.....	8	I.c.....	14	3	6-7	3	Yolk sac	Yolk sac	
			8	I.c.....	14	1	6	5				
			3	I.c.....	14	3	6-7	3	CHA	CHA		
			6	CHA.....	3	3	6-7	3	Amniotic fluid	Amniotic		
			6	Amniotic.....	3	1	6	5	Yolk sac	Yolk sac		
			7	Yolk sac.....	5	1	6	5				
			7			1	6	5				
			7			1	6	5				
			7			1	6	5				

* The expansions of abbreviations used are as follows: i.d., intradermal; i.c., intracerebral; i.n., intranasal; i.p., intraperitoneal; CHA, chorioallantoic membrane. † This material was sterile for bacteria.

materials were obtained (cases 1, 5 and 6) or else the materials were stored in a cold box (solid carbon dioxide) in sealed glass containers for variable periods until used (case 4, fatal case). The studies carried out on material from each case are recorded in summary form in the table.

The results were uniformly negative. In 1 monkey a few tiny vesicles developed on the penis a week after inoculation on the skin of the penis with material from case 4. However, the involved skin was passed to another monkey in which lesions did not develop. Moreover, lesions were not observed in 3 other monkeys inoculated on the penis with lung suspension from the fatal case.

With all material employed and by all routes of inoculation some deaths of embryonated eggs occurred at irregular intervals after inoculation. Some of these deaths were due to trauma and others to bacterial contamination. Numerous histologic sections were examined after staining with hematoxylin and eosin and with Giemsa stain. In no instance were inclusion bodies or other specific lesions recognized.

COMMENT

The chief features of interest in these 6 cases of erythema multiforme exudativum was the occurrence of pneumonia in 3 of them. Lesions in the respiratory tract have been described by previous authors, but their prominence as an essential feature of the disease has not been emphasized. The pharynx, epiglottis, vocal cords and trachea are not infrequently involved by the process which so prominently involves the mucous membranes of the oropharynx. In a fatal case^{21d} there was ulceration of the epiglottis, the vocal cords were denuded, and the tracheal mucosa showed small ulcerations with the hemorrhage. Another case, at autopsy, showed "acute diphtheritic pharyngitis" and an "area of diphtheritic ulceration" on the larynx.^{18b}

Involvement of the bronchi and the pulmonary parenchyma is not uncommon. Pneumonia was present in 3 of 16 cases in one series.^{15b} Markham³³ mentioned 5 cases in which there were "atypical virus pneumonia" and lesions of the skin, mouth, eye and penis. In 2 of 3 cases of "atypical" ulceromembranous stomatitis reported by Henry,¹⁰ there was clinical and roentgenographic evidence of pneumonia. Finland observed a number of cases with pneumonia, 3 of which were fatal.³⁹ Several others have also reported cases with physical signs and roentgenographic evidence of pneumonia.⁴⁰

In 1 of the cases of Stevens and Johnson the diagnosis "broncho-pneumonia" was made by physical examination.⁸ Another patient had

39. Finland, M.: Personal communication to the author.

40. Lever.^{4c} Haddad.¹¹ Erger, B. D.: Erythema Multiforme Pluriorificialis (Stevens-Johnson Disease), *Mil. Surgeon* 95:308-312, 1944.

rales, but a roentgenogram of the chest was not taken.^{14a} In the majority of reported cases the lungs were either not mentioned at all or were described as clear on physical examination but roentgenograms of the chest were not reported.

On the basis of the present series, and from a consideration of the previously reported cases, it seems probable that pneumonia occurs more often in this disease than has been recognized hitherto. The situation appears to be somewhat analogous to that of primary atypical pneumonia; in both conditions the physical signs are not those of consolidation and the rales that are detected are readily discounted and ascribed to "bronchitis." It is now well accepted that instances of mild primary atypical pneumonia can be recognized only by roentgenograms in a considerable percentage of cases. It appears probable that a similar difficulty attends the diagnosis of the pneumonia associated with erythema multiforme exudativum.

There is little available information on the pathologic nature of this pneumonia. Four cases have been reported in which pneumonia was found at autopsy. In 1 case, in which death occurred five weeks after onset, autopsy disclosed "partly suppurative, lobular, pneumonia."²⁰ In another case, in which death occurred more than a month after onset, and at a time when the cutaneous and oral lesions were practically healed, there was denudation of the larynx and there was ulceration of the epiglottis, trachea and both main bronchi. The lungs themselves were hyperemic and contained bluish black, nonaerated areas.^{21d} In a third case, death occurred a week after onset; autopsy disclosed "severe diffuse purulent bronchitis and bronchopneumonia." It was also noted that there were "many colonies of streptococci on the lumen" of the bronchi.^{18b}

In a 9 year old girl who died six days after onset, the larynx, trachea and bronchi showed congestion and the lungs were heavy and atelectatic with areas suggestive of early pneumonia. Severe atelectasis was seen throughout both lungs. Areas of pronounced pulmonary edema with escape of blood into the alveolar lumen and collections of polynuclear cells in some alveoli were noted. The bronchial walls and the alveolar and pleural capillaries were congested.^{15b}

None of these reports included a detailed description of the appearance of microscopic sections of the lungs.

A reasonable suggestion as to the pathogenesis of the bronchopulmonary involvement in this disease must take into account the likelihood that the lesions in the respiratory tract are similar to those on the visible mucous membranes. The available descriptions, quoted herein, support this suggestion. In this connection, the report of Poole and

Wehger⁴¹ on the pulmonary pathologic changes associated with exfoliative dermatitis is of possible relevance. These authors reviewed the observations at autopsy in cases of exfoliative dermatitis and regularly found desquamation of the epithelium of the trachea, bronchi, bronchioles and alveoli. They concluded that death was not due to pneumonia but to obstruction of the respiratory passages, causing suffocation.

The pneumonia of erythema multiforme exudativum may be of a similar nature, since it is altogether likely that the mucosa of the tracheo-bronchial tree is involved to greater or less degree by a vesiculobullous eruption identical with that seen in the mouth. However, the clinical observations in the present group of cases do not entirely support this theory of the pathogenesis of the pulmonary lesion. In case 1 the pneumonia probably antedated the visible eruption, and in case 2 it clearly preceded the eruption on the skin and mucous membranes. In exfoliative dermatitis, on the contrary, the signs of pulmonary involvement appeared late in the illness. Moreover, in the present series of cases there appeared to be no relationship between the occurrence of pneumonia and the severity of the lesions of the skin and the mucous membrane. In case 3, in which there was pneumonia, the illness was otherwise the mildest in the series from the point of view of the height of fever and the extent of involvement of the mucous membranes. On the other hand, the disease in case 4 was the severest in the group, in terms of fever and the extensive involvement of the mouth and eyes. Clinically, in this case, the larynx was severely affected and there was some evidence of bronchitis, but pneumonia was not demonstrable either clinically or by roentgenogram.

Further evidence against the suggestion of obstruction of the respiratory passages resulting from denudation of the epithelium was the absence of signs or symptoms of respiratory distress in the cases in this series. Only one patient (case 2) had moderate dyspnea and slight cyanosis. In none of the cases was there clinical or roentgenographic evidence of atelectasis. Likewise, in previously reported cases, including those with rales, and those with clinical and roentgenographic signs of pneumonia, indications of respiratory embarrassment were rarely mentioned.

Many of the features of the pneumonia in the present series of cases bore a close resemblance to primary atypical pneumonia. The prodromal symptoms, absence of physical signs of consolidation, the character of the radiographic lesion, the minimal degree of respiratory distress, the absence of pleural pain or bloody sputum and the relatively normal leukocyte count were features not unlike those commonly encountered

41. Poole, A. K., and Wehger, R. T.: Fatalities in Exfoliative Dermatitis, *J. A. M. A.* **102**:745-751 (March 10) 1934.

in primary atypical pneumonia. In 2 of the 3 cases with pneumonia tests for cold hemagglutinins were made, and in both a significant titer was found. In the 3 cases without pneumonia, the test was performed in 2 and in both the result was negative. With present knowledge, it would be unwarranted to regard this test as specific or diagnostic for primary atypical pneumonia. The clinical and roentgenographic observations in the cases reported, however, suggested a resemblance between the pneumonia associated with erythema multiforme exudativum and primary atypical pneumonia.

Bacteriologic studies in the majority of reported cases have not yielded results suggestive of a causal relationship. This was true also in the present series. In case 3, however, bacteriologic and serologic evidence of beta hemolytic streptococcus infection was secured. While it is improbable that this organism represents the usual cause of the clinical picture of erythema multiforme exudativum, it is possible that it may be one of the causes. In the present case, however, it is believed that the patient had a concurrent infection with hemolytic streptococcus. Other examples of what was thought to be concurrent infection with two agents of respiratory disease have been presented elsewhere.⁴²

The studies carried out in animals and embryonated eggs were probably adequate to rule out the presence of the viruses of herpes simplex, vesicular stomatitis and members of the psittacosis-meningo-pneumonitis group in the materials tested. No etiologic agent was found. These studies neither rule out nor support a possible virus causation for cases of erythema multiforme exudativum.

SUMMARY

The severe form of erythema multiforme exudativum, with predominant involvement of the mucous membranes of the mouth, eyes, and urethral meatus, is a clinical entity. Its etiology is unknown. Although it is believed to be an infectious disease, bacteriologic studies and the results of inoculations of animals have yielded negative results. Nonbacterial pneumonia occurs frequently in this condition and is believed to be an integral feature of the disease. In its clinical features, it bears a rather close resemblance to primary atypical pneumonia.

NOTE.—Since this article was submitted for publication attention has been directed to a report by J. H. Stanyon and W. P. Warner entitled "Mucosal Respiratory Syndrome," *Canad. M. A. J.* 53: 427-434 (Nov.) 1945. This report deals with 17 cases of the severe form of erythema multiforme exudativum. An excellent clinical description of the cases is given. Of particular interest was the demonstration of nonbacterial pneumonia in 14 of the cases. There were 2 fatalities in

42. Commission on Acute Respiratory Diseases: Association of Acute Pulmonary Lesions with Infections of the Throat, to be published.

the series; a detailed description of the pathologic findings in 1 case is included. The principal abnormal findings were in the lungs, which were almost completely consolidated but which differed in their appearance from ordinary bronchopneumonia or lobar pneumonia. Microscopic study showed the inflammatory exudate in the lungs to be of an essentially mononuclear type. The authors concluded that the pneumonia was an integral feature of the syndrome and that its cause was not bacterial and was probably viral.

ADDENDUM.—Further attempts to isolate an agent from the lung in the fatal case reported here were carried out by Dr. H. W. Schoening of the Bureau of Animal Industry, United States Department of Agriculture. Horses, cows, sheep, pigs and guinea pigs were employed. Normal animals, as well as animals immune to the New Jersey and Indiana types of vesicular stomatitis virus and to the virus of ovine ecthyma, were inoculated. No lesions were produced in any of the animals inoculated nor did exposure to material from the lung in any way affect the susceptibility of the previously normal animals to the two types of vesicular stomatitis virus.

The following officers, while at Fort Bragg, helped to make this study possible: Brigadier General H. C. Coburn, Jr., Medical Corps, Surgeon, Fort Bragg; Colonel R. T. Arnest, Medical Corps, Surgeon, Fort Bragg; Colonel G. D. Chunn, Medical Corps, Commanding Officer, Regional Station Hospital; Colonel J. N. Williams, Medical Corps, Commanding Officer, Regional Station Hospital; Colonel W. B. Daniels, Medical Corps, Chief of Medical Service; Lieutenant Colonel J. M. Kinsman, Medical Corps, Chief of Medical Service; Colonel A. Blumberg, Medical Corps, Chief of Laboratory Service, and Mrs. Ann Alvey, Pathological Laboratory Technician.

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BEHAVIOR AND PSYCHOLOGIC PROBLEMS OF YOUNG DIABETIC PATIENTS

A Ten to Twenty Year Survey

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AND

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IT IS the purpose of this paper to describe the behavior and the psychologic problems of a group of diabetic patients who have been observed from childhood through adolescence and early adulthood. All these patients were under treatment for from ten to twenty years. It is well known that normal children exhibit temporary alterations in behavior in the transition from childhood and adolescence to adult life. However, these alterations are more pronounced in diabetic children because of the abnormal regimentation to which they are subjected and because of certain psychic and physical factors associated with their condition.

MATERIAL

Forty-three patients were studied, 22 females and 21 males (table 1). Thirty-four of these patients attended the outpatient department at the Mount Sinai Hospital, and 9 were private patients. The former were treated in the pediatric clinic until they reached the age of 14, when they were transferred to the clinic for adult patients. Most of the children were from poor or lower middle class homes. Many had been receiving financial aid from government or private agencies. Even in cases in which the economic status was not that of the lower income bracket, the care and special needs attendant to the maintenance of adequate diabetic treatment often brought the families into the submarginal economic group.

As soon as a diagnosis of diabetes had been made, the patient was admitted to the wards of the hospital for regulation. At that time the child and the parents were instructed in the dietary calculations, the administration of insulin and the management of the diabetes.¹ Many cooperative children, whose diabetes was easily regulated, required no further hospitalization. On the other hand, when the patients or their parents were uncooperative, the diabetes was poorly controlled and frequent readmissions because of ketosis were necessary.

All the patients in this study were 12 years of age or younger at the onset of diabetes. The youngest was 11 months old. The diabetes started during the first five years of life in 9 of the children, between 5 and 9 years in 17 of them and between 10 and 12 years in 17 of them. Twenty patients were under continual

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1. Fischer, A. E.: A Diabetic Primer for Children, New York, privately printed, 1938.

TABLE 1.—Survey of Forty-Three Diabetic Patients

Patient	Sex	Case	Age at Onset of Diabetes	Duration in Years	Dominant Behavior	Occupation
M. B.	F	1	3	16	Dependent	Secretary
P. B.	F	2	10	10	Introverted, slovenly	Clerk
B. B.	F	3	11	19	Aggressive, euphoric	Salesgirl
M. B.	F	4	5	13	Depressive	None
H. C.	M	5	8	12	Self reliant, independent	Clerk
S. E.	M	6	4	15	Independent	Student
N. G.	M	7	11	13	Aggressive, independent	Furrier
R. G.	M	8	11 mo.	17	Submissive	Student
I. G.	M	9	8	12	Aggressive	Student
S. G.	F	10	9	18	Self reliant, inclined to be depressed	Housewife
E. H.	F	11	12	17	Submissive, dull	Housewife
B. H.	M	12	11	16	Suggestive of bravado, euphoric	Watchmaker
E. H.	M	13	9	13	Normal	Student
G. H.	M	14	11	14	Dependent	Salesman
A. I.	M	15	10	18	Depressive	Mechanic
H. I.	M	16	10	17	Aggressively independent	Salesman
M. J.	F	17	9	16	Normal	Secretary
M. K.	F	18	11	16	Normal	Housewife
G. K.	F	19	10	13	Normal	Salesgirl
R. K.	F	20	11	13	Depressive, insecure	Secretary
D. K.	F	21	7	12	Apathetic, indifferent	Maid
J. L.	M	22	14½	18	Rebellious, indifferent	Business
S. L.	F	23	6	13	Rebellious	Student
C. L.	M	24	4	19	Dull, submissive	Clerk
A. L.	M	25	2	14	Dull	Student
E. L.	M	26	8	12	Aggressively independent	Lens grinder
S. M.	F	27	12	13	Insecure, depressed, schizoid	Stenographer
E. M.	F	28	3	16	Normal	Student
J. M.	M	29	6	18	Normal	Clerk
A. N.	M	30	11	14	Self reliant, aggressive	Truckman
M. P.	M	31	4	18	Infantile, euphoric	Butcher
E. S.	M	32	12	10	Normal	Clerk
M. S.	F	33	4	11	Resigned	Student
L. S.	M	34	7	15	Sullen, negative	Butcher
A. S.	F	35	6	15	Dull, submissive	None
S. S.	F	36	8	16	Rebellious against diabetes and society	Salesgirl
G. S.	M	37	10	15	Indifferent	Mechanic
E. S.	F	38	9	16	Dependent	Secretary
M. S.	F	39	6	12	Normal	Salesgirl
D. T.	F	40	5	13	Normal	Student
J. T.	F	41	10	12	Temperamental, unhappy	Office worker
M. T.	M	42	6	17	Normal	Machinist
J. Z.	F	43	10	15	Dull, submissive	Housewife

observation for at least ten years and 23 for from fifteen to twenty years. All were American-born children, the majority of Russian-Jewish origin and the others of Italian, Irish or Scandinavian descent.

The family and social histories were carefully investigated, and continued contacts with the family were maintained; consequently, all the significant factors which might influence development were made known to us. These contacts with our patients became so intimate that we were family advisers to many of the group, especially with respect to education, occupation and marriage. Our case records were very complete and included reports of the child's progress at school and at home. Special note was made of the metamorphosis which always takes place during adolescence.

GENERAL FACTORS INFLUENCING BEHAVIOR

The general factors which influenced the behavior of diabetic children were similar to those which operated in other chronic illnesses, such as asthma or rheumatic heart disease. These factors were concerned primarily with the reactions which were evoked in the family circle, at school or in play.

1. *The Family*.—As in all children, home environment and the relationship between the members of the family greatly influenced the diabetic child's behavior. The financial status of the home and its emotional stability were equally important influences. Most of the patients came from underprivileged families or families with low income. The financial burden of caring for a chronic illness such as diabetes imposed an unusual strain on these families. Economic insecurity and its sequelae of tension and discord in the home were shared by the children. Not infrequently, rejection of the diabetic child was voiced because its care became an unwanted burden. Such an instance was the following case.

E. L. (case 26), diabetic since the age of 8 years, was the son of divorced parents. He and his mother occupied a single room where he witnessed prostitution and intoxication. At times his mother kept him out of their "home" so that she could pursue her profession. Suicidal tendencies developed in this child. On one occasion he deliberately withheld insulin for a week, hoping to die in diabetic coma. During a period of hospitalization we were able to convince the mother of the advantage of placing him in a foster home.

Few children realized the implications of the diagnosis of diabetes. They accepted their condition passively at first, unaware of the restrictions which it might place on them later. The parents, on the other hand, were always greatly shocked. They asked first whether their child would live, and if so, for how long. When reassured, they usually asked why the affliction had occurred and how it could have been avoided. They assumed generally that the child's diet had been at fault and blamed themselves for permitting an excessive intake of carbohydrate. They inquired as to the influence of heredity, namely, what part it played in the transmission of diabetes and how it might

affect further progeny of their own and that of the diabetic child. Soon after the initial shock had worn off, the education of the parents in the care of the diabetic child began. This process tended to lessen the anxiety by permitting the parents to share in a program which aimed to restore the child's well-being. The mother usually assumed the role of dietitian. Many children learned to administer insulin themselves. Some of them were afraid or unwilling to do so; the mother or the father then performed the injecting.

There were two common parental reactions, one being an oversolicitous coddling and pampering attitude and the other one of resentment and rejection. The former usually produced a submissive, dependent type of child and the latter a belligerent character. However, sometimes the early training in diabetic management, which led understandably to an overzealous or overprotecting attitude on the part of the mother, eventually evoked rebellion on the part of the child. Such patients all too frequently were cooperative at first, but like those children who felt rejected, soon resented the restrictions placed on them. Examples of the various behavior patterns follow:

1. *Oversolicitude, Producing Dependency:* R. G. (case 8) was a boy whose diabetes began when he was 11 months old. The onset at so unusually early an age accounted in part for the intense anxiety and exaggerated solicitude with which he was regarded. In addition, the parents nurtured this boy with special attention because their only other child was a deaf-mute. He was sheltered to an unusual degree throughout childhood and adolescence. This patient has been the most docile and submissive of all the male diabetic persons in the group. Now 20 years old, he is beginning to display signs of independence and self reliance for the first time.

2. *Rejection, Producing Resentment:* H. I. (case 16) had had diabetes since he was 10 years old. His parents were unintelligent and illiterate and were unable to understand the instructions for his care. The patient had always been difficult to manage. Insulin was given irregularly, and the boy frequently would leave home at night. He was delinquent at school. He was transferred to a foster home at the age of 12 so that the diabetes could be treated more successfully and in a less disturbed atmosphere. At first he was happy, and his behavior improved remarkably. However, after a year he reverted to his previous behavior, and in spite of a change in foster homes his conduct remained unsatisfactory. On occasion he would return to his own family, even though he fought with his brother continually. At times he had a euphoric, devil-may-care attitude. At other times he felt rejected, displayed a morbid attitude and stated at 17 years of age that he would rather die than live the restricted, handicapped life of a diabetic person. His case history is completed on page 722.

3. *Overprotection, Producing Rebelliousness:* J. L. (case 22) became diabetic when less than 2 years old. During his early childhood he had many illnesses—pneumonia on several occasions and recurrent otitis media and mastoiditis. His diabetes was difficult to control and he was hospitalized on several occasions. The child's father had severe asthma. The mother spent most of her life caring for her husband, who frequently was unemployed, and for her diabetic child. She took the boy to school and called for him daily. She rarely permitted him

to cross a thoroughfare alone. As he grew older, he began to show resentment against her overprotection. On one occasion he was injured when he fell off a truck on which he was riding. This accident served to increase his mother's watchfulness. Recently, at the age of 20, he decided to marry. His mother's chief concern was his inability to give himself his insulin. Yet she has never permitted him to do so, fearing that he would not measure the dose correctly. The boy recently said, "What does she want to do, come along with me on my honeymoon?"

Some parents awakened their children at night, ostensibly to have them void but actually to make certain that they were not in insulin shock. What most of these parents really feared was that death might result from an unrecognized and untreated reaction to insulin. Many children passed through a period of hypoglycemia during sleep—some could not be roused in the morning. When such episodes occurred early in the course of their diabetic experience, the parents of these children became extremely fearful. As a result, many of the mothers slept in the same bed with their children so that they might detect tremors or unusual perspiration which signified the onset of a hypoglycemic reaction during the night. The potential dangers of this practice are self evident, especially when carried through adolescence.

The presence of a diabetic child among normal siblings introduced a threat to the security of both the normal and the diabetic child. The normal child usually resented the extra care and attention which the diabetic child received. On the other hand, the presence of a normal sibling, receiving the natural affection of the parents, evoked an even greater feeling of insecurity in the child who felt stigmatized by the handicap of the diabetes. Mothers found it burdensome to prepare separate meals for their children. Resentment was aroused, and the feeling of "difference" was continually accentuated when the other children were permitted to eat unlimited portions of food, especially sweets, which the diabetic child was denied.

A unique situation occurred when in one of identical twins, M. S. (case 33), diabetes developed at 4 years of age, the sister remaining unaffected. Before the onset of diabetes the twins always had eaten their meals together. After Mildred was subjected to the diabetic regimen, she refused to permit her sister, Helen, to leave her sight for fear she would receive extra food. As a compromise both children were placed on a diabetic diet, but the mother continued to offer the nondiabetic child extra food at opportune moments. This stratagem was necessary in order to maintain harmony at home. It was only after puberty that the problem of food became less acute. Only then did the diabetic girl apparently accept her dietary restrictions and become satisfied to have her sister eat with the rest of the household while she, meanwhile, preferred to eat alone rather than be restricted at the family table.

2. *School and Play Groups.*—The associations in school and at play were almost as important as those of the home in influencing the behavior of the diabetic child. Activities in school and at play introduced new forms of competition. All children are eager to hold their place among their schoolmates. This feature of childhood raised two problems for the diabetic child: 1. Could a feeling of "difference" be avoided? 2. Could the diabetic child participate in all activities? While some children did not regard diabetes as a handicap and were not embarrassed by their friends' knowledge of it, others concealed it from their playmates. For example, many children refused to take nourishment to school since it emphasized their feeling of "difference." Girls, more often than boys, found it difficult to be casual about their condition, and their friends often did not learn of the diabetes, except by chance. Such girls lived in constant dread lest the diabetes be discovered. They carefully hid their syringes, saccharin and insulin and hoped that their dietary restrictions would remain unnoticed. Nevertheless, their painstaking efforts often were thwarted. One girl lost her best friend because the latter accidentally learned of the diabetes from their teacher. This attempt at concealment was considered a breach of confidence between two close friends. Another patient became confused when her handbag was opened by a friend who found that it contained insulin and a hypodermic syringe. Another awkward situation arose at a patient's home when a visitor opened the refrigerator, found insulin on a shelf and inquired as to its purpose. Such examples illustrated the need for urging all diabetic children to be frank about their condition and to explain to their friends the reasons why they were restricted.

Even when a wholesome attitude toward diabetes existed, insecurity could not be avoided. Some children could not participate fully in all competitive sports. The caloric intake of many of these children was somewhat below that of physically active nondiabetic children of their own age, as it was not always possible to supply a diet which permitted maximum exercise and yet was compatible with good diabetic control. This was the accepted practice during the earlier period of this study. Some children could not play strenuously, go on hikes, ride bicycles and engage in other activities because they lacked the extra physical capacity. They were compelled to offer excuses, and this accentuated their feeling of "difference." The observance of religious functions, such as the Jewish Holy Days, Holy Communion, or Lent interrupted the usual insulin-diet schedule, thereby not only interfering with the medical control but also emphasizing the limitations which diabetes imposed on the child. The camp for diabetic children enabled the patients to join one another in physical activities and thus broke down the feeling of isolation by being in a homogeneous group. On the other

hand, a few children resented the stigma attached to the name "diabetic camp" and refused to attend.

3. *Adolescence and Maturity.*—The young nondiabetic child is trained to a more or less routine life largely within the confines of the home. His meals are nearly always eaten at home; his sleeping hours are regular, and his social life is simple. It is not difficult, therefore, to transform the daily routine of a nondiabetic child to the diabetic regimen. One can understand why excellent diabetic care is possible with young patients, for only after the child acquires greater contacts with the outer world does good control become increasingly difficult. The dependence of childhood often was replaced by independence during adolescence, which increased as the patient became self supporting

Most adolescents became increasingly resentful of others' awareness of their condition. They refused to have their teachers or prospective employers know of their disease, for they wished to be considered "equal" in a competitive world. This was especially true among the girls, for whom adolescence normally is a more difficult period of adjustment. When their friends discussed marriage, they were embarrassed and distressed. Many of them feared that diabetes would interfere with their chances of getting married and having children.

Some of the boys, assuming that they would be rejected for military service, sought to evade detection of the diabetes by taking large amounts of insulin prior to their induction examination. A few succeeded in passing the initial examination and were accepted, but unfortunately for them they were detected within a few days and discharged from the army (E. L., case 26). As a group they, like other outwardly healthy-looking boys, were embarrassed when questioned as to why they were not in military uniform. S. E. (case 6), who had been classified "4-F," became embroiled in a fight when accused of being a slacker.

In general, however, the influence of maturity on the diabetic patient has been favorable. With the approach of adult life the adjustments and the behavior of most patients improved. Even those patients whose outlook seemed rather hopeless during the teens fared surprisingly well when they were able to escape the sinister and retarding influence of a poor childhood environment.

SPECIFIC EFFECTS OF DIABETES ON BEHAVIOR

1. *Duration of Diabetes and Age of Onset.*—McGavin, Schultz, Peden and Bowen² stated that the earlier the child had diabetes the more readily he or she accepted it emotionally as part of the growing-up

2. McGavin, A. P.; Schultz, E.; Peden, G. W., and Bowen, B. D.: The Physical Growth, the Degree of Intelligence and the Personality Adjustment of a Group of Diabetic Children, *New England J. Med.* **223**:119 (July 25) 1940.

process, whereas those in whom it developed at a later age tended to rebel against it. Loughlin and Mosenthal,⁸ on the other hand, reported that the earlier the onset of diabetes the greater was the tendency toward personality changes. An analysis of the age of onset of the diabetes and its duration for our 43 children, all of whom had it before 12 years of age, revealed no relationship between either the duration of the disease or the age of onset and the type of behavior. We could find no consistent difference in the degree of personality change between those in whom diabetes developed in early childhood (before the age of 6 years) and those in whom it developed between 6 and 12 years of age.

2. *Severity of Diabetes*.—Increasing amounts of insulin were needed in nearly all instances as the children matured. Some patients required large amounts of insulin (up to 150 units a day). These children displayed some anxiety because their dose had increased. However, there was no correlation between behavior and the severity of the diabetes as judged by the requirement of insulin.

3. *Regimentation of Diabetic Patients*.—During the 1920's and 1930's, when regular insulin was the only type available, a rigid regimen was required. Frequent daily injections of insulin and accurate weighing of food were necessary. At that time the use of a lower carbohydrate content of the diet was the prevailing practice. The early years of treatment of many of our patients were characterized by a high degree of consciousness of their diabetic condition. This sometimes led to subterfuge. Most patients refused to adhere to a weighed diet. The infractions were often minor, yet if children were not allowed sufficient variety and adequate caloric intake they would supplement the diet surreptitiously with candy or other sweets. Many patients reduced their intake of food just prior to medical examination, hoping thereby to submit a sugar-free urine. Occasionally, urine diluted with water was presented for analysis.

The importance of checking such minor infractions was obvious. Prescriptions for insulin and diet based on false reports led to a lack of correlation between the assumed and the actual diabetic condition. As a result, accurate "diabetic control" became impossible. The physician found himself unable to explain certain clinical and laboratory data, and the patient realized that the physician could be fooled. This encouraged the patient further, and if the physician was not on guard at each visit, complications such as ketosis might arise in spite of apparently careful supervision. Today the diet is more liberal; the number of injections are fewer because of longer-acting insulins, and regimentation has been minimized.

3. Loughlin, W. C., and Mosenthal, H. O.: Study of the Personalities of Children with Diabetes, *Am. J. Dis. Child.* 68:13 (July) 1944.

We encouraged independence and self reliance by having the patients administer the insulin and regulate the diet themselves. In the first months of treatment the initial instructions were followed meticulously; the diet was weighed, urinalyses were made frequently and injections of insulin were given accurately. Then, after a few years the patients became careless, and the diet was estimated but not weighed. Subsequently, the urinalysis alone was used as a guide to the amount of insulin needed, little attention being paid to the type and the amount of food consumed. Finally, some patients completely disregarded their dietary prescriptions and omitted urinalyses, the dose of insulin being regulated merely by the way the patient "felt." In defense of their behavior most of the adolescent patients stated that they "felt better and stronger" when they had glycosuria and "weaker" when they were sugar free. They thought it logical therefore to eat freely and excessively, and they disregarded the glycosuria. An attitude of bravado, not peculiar to diabetic children alone but characteristic of adolescence in general, appeared in an exaggerated form at this time. Nevertheless, even careless patients rarely failed to take their daily dose of insulin.

4. *Hypoglycemia*.—We regard hypoglycemia with anxiety and do not agree with those who have a complacent attitude toward it, for the harmful effects of hypoglycemia on behavior are both immediate and delayed. Cerebral changes can be demonstrated by the electroencephalogram, which reveals abnormalities in some diabetic children not only during hypoglycemia but also for some time after the blood sugar level has risen above normal.⁴ These changes may be due either to anoxia or to metabolic effects secondary to hypoglycemia.

Immediate Effects: The usual symptoms of hypoglycemia, such as pallor, sweating, dizziness and tremors, are well known. It has not been recognized generally that young children also become irritable and fretful. Failure to understand the basis of such erratic conduct of young children often started a chain of circumstances which affected future behavior patterns. These children were scolded or punished because of actions beyond their control. On the other hand, others learned to simulate the symptoms of hypoglycemia in order to obtain extra sweets or to escape from an unpleasant situation. We have also known children who frequently feigned reactions to insulin in order to avoid school, especially at examination time.

The older children and adolescents exhibited the commoner symptoms of hypoglycemia, such as confusion, negativism and violent outbursts. The occurrence of hypoglycemia in public often led to embarrassment. Some children had convulsions and became unconscious in the presence of their playmates. One patient, N. G. (case 7),

4. Strauss, H., and Fischer, A. E.: To be published.

while in a hypoglycemic state attacked a pedestrian and was placed under arrest.⁵ Another boy, A. N. (case 30), undressed on the street while in a state of insulin shock. Erratic behavior sometimes occurred at school, and teachers were confused by the bizarre responses not typical of the child. Sometimes patients displayed abnormal behavior only during late afternoon hours when, after an inadequate lunch or strenuous exercise, the blood sugar fell to hypoglycemic levels.

Delayed Effects: Repeated hypoglycemic reactions over a long period may affect cerebral function, with consequent mental deterioration. This process is a slow, cumulative one which may not be demonstrable for years. Unrecognized hypoglycemic episodes may occur during sleep. Cerebral deterioration may be explained on the basis of such reactions in addition to those which occur and are recognized during the day.

There were several patients who had frequent and prolonged reactions to insulin over a period of years and who no longer displayed their original intellectual capacity.

S. E. (case 6) asserted that his memory and concentration at 20 years of age were not so acute as they had been during elementary and preparatory school years.

S. L. (case 23), 20 years old, felt chagrined because she barely passed college examinations. She stated that she was stupid, was unable to study properly and felt that she was not nearly so apt as during her earlier schooling.

The following children presented severer disturbances.

B. B. (case 3) became diabetic at 11 years of age. At that time she was a healthy happy girl of average intelligence. She deteriorated progressively until, at 29 years of age, she was euphoric and almost moronic.

M. B. (case 4), who was a child of average intelligence at the onset of the diabetes, exhibited mental deterioration and dulling of the intellect following repeated severe reactions to insulin. She was considered to have had epilepsy and died during a seizure. At autopsy the brain revealed diffuse gliosis of the cortex and subcortex, indicating degenerative encephalopathy. These findings were similar to those reported by Root and Styron.⁶

The question arises as to whether repeated episodes of hypoglycemia may precipitate underlying epilepsy or whether hypoglycemia may produce sufficient damage to cause epileptiform seizures.⁷ While the significance and the treatment of reactions to insulin have been stressed repeatedly, we feel that the potential dangers from many such recurrent episodes have not been emphasized sufficiently.

5. Adlersberg, D., and Dolger, H.: *Medico-Legal Problems of Hypoglycemic Reactions in Diabetes*, *Ann. Int. Med.* **12**:1804 (May) 1939.

6. Root, H. F., and Styron, C. W.: *Insulin Hypoglycemia and Vascular Accidents in Diabetes Mellitus*, *J. Mt. Sinai Hosp.* **8**:953 (Jan.-Feb.) 1942.

7. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: *Treatment of Diabetes Mellitus*, ed. 7, Philadelphia, Lea & Febiger, 1940, p. 498.

5. *Complications.*—Children did not worry about possible complications. Adolescents, however learned of them through reading and through contacts with older diabetic patients. The various manuals for diabetic persons have stressed the more serious complications arising in older diabetic patients and all too frequently have alarmed the young patients.

Diabetic complications affected the patients by interfering with normal life and by causing anxiety and depression. This was especially true of ocular complications, such as cataracts and retinopathy, which bear the threat of blindness. It was tragic to have survived fifteen years of childhood diabetes, to have learned a trade and then to become blind.

Furunculosis and other intercurrent minor infections which could be cared for at home did not, as a rule, change the daily routine. However, severer suppurative infections did interfere with attendance at school and at work. Hospitalization was required for any infection accompanied with ketosis and occasionally for complications of a degenerative nature.

Two patients had active pulmonary tuberculosis, G. H. (case 14) and E. L. (case 26). G. H.'s infection was arrested; he married and became self supporting. E. L. contracted tuberculosis after an unsuccessful marriage and has advancing lesions requiring institutional care.

Acne, sometimes severe, occurred in almost all the male patients during puberty. It naturally caused considerable embarrassment and added to the problems of adolescence.

Atrophy or hypertrophy of the subcutaneous fat⁸ due to injections of insulin proved a disturbing factor, especially in girls. They wore long-sleeved dresses in order to conceal the deformed areas and avoided swimming because of the appearance of the thighs. The condition in some of the children seemed to improve following puberty. It was hoped that the introduction of protamine zinc insulin would reduce the incidence of tissue deformity. Unfortunately, this was not the case, for tissue reactions have continued to appear with the newer modifications of insulin.

Short stature existed in some patients and in a few led to minor behavior disturbances. Fortunately, none of our patients exhibited so-called diabetic dwarfism. Boys were more conscious of their short stature than girls. H. C. (case 5), hoping to become taller, slept with his feet tied to a weighted pulley at the foot of his bed and with another rope around his waist which pulled his trunk in the opposite direction.

8. Fischer, A. E.: The Frequency of Atrophy of the Subcutaneous Fat Following the Injection of Insulin, *Am. J. Dis. Child.* **38**:715 (Oct.) 1929.

6. *Development of Abnormal Behavior.*—A number of patients exhibited pronounced behavior changes over a period of years. These included bellicose acts, euphoria, wanderlust, alcoholism, fatalism, depression and suicidal trends. Fortunately, in the majority of instances these aberrations were transient. However, 2 patients displayed distinct psychopathic tendencies severe enough to warrant institutionalization. Their case histories in brief follow.

S. M. (case 27) had been diabetic since 12 years of age. Her family was constantly in dire economic straits. The father was a pushcart peddler who worked irregularly. The main support of the family came from charitable organizations and relief agencies. Although of more than average intelligence (an intelligence quotient of 112 at 19 years of age), the patient could not complete high school successfully. She was always reserved and uncommunicative. It was noted that she seemed unmoved by any scolding from either parent. At 19 she first displayed frank schizophrenic behavior by locking herself in her room for almost two weeks, talking to no one and refusing to wash herself. She directed a number of threatening letters of paranoid type to the physicians and the social workers, and she was transferred, subsequently, to a psychiatric institution.

L. S. (case 34) was the only son in a family which included four daughters. The father, a truck driver, was devoted to his family. The mother was a dull-witted but conscientious woman. Once, when confronted by her son's teacher with a report of poor grades in school, she blandly remarked that it made little difference how he fared in school inasmuch as he could not live long! The four sisters were pleasant, well adjusted girls who were devoted to their brother. They gave him the best room in their home, the six other members of the family crowding together in two rooms. The family had moved to the city from a rural area in order to provide better diabetic care for the boy.

Despite all this affection and attention, the patient remained an aloof, undemonstrative child. Neither physicians nor social workers were able to establish a close relationship with him. He left vocational high school in order to earn \$8 a week as a butcher's helper. A set of polished butcher knives hung in a case on the wall of his room. Several times he was known to have expressed homicidal threats, not directed against any particular person. The definite schizoid pattern became more apparent as he passed through adolescence and at 18 years of age he was referred to a psychiatric institution. His intelligence quotient at age 17 was 89.

An attempt to escape regimentation resulted in wanderlust and in alcoholism in several patients.

M. P. (case 31), en route from Chicago to New York, suffered a severe reaction to insulin in Ohio. After recovery in a small hospital there, he found the surroundings so pleasant and the grass so green that he remained at the hospital until his funds were exhausted. He stated that it was the first time that he had ever known such luxury.

H. I. (case 16), (whose early history was cited on page 714, decided after graduation from high school to return home, but stayed only a short time, quarreling constantly with his mother and sisters. He then lived in rooming houses, making a living by selling magazine subscriptions. He traveled through the South by bus and truck. He held many positions for short periods and finally returned to New York complaining of failing vision. He reentered the hospital, where it was found

that he had extensive retinitis. He threatened to commit suicide and nearly succeeded by omitting insulin for a week. However, he recovered from diabetic coma and with the aid of excellent social service was rehabilitated. He lived in a dormitory for the blind, made a remarkable adjustment and became self supporting, selling stockings to nurses and to hospital employees. He recently married a nurse much against the wishes of both families. The only witnesses at the ceremony were his physician and a social worker.

S. E. (case 6), an adolescent, who learned to play several musical instruments, joined a jazz band and, at the age of 14, began to drink excessively.

E. L. (case 26), whose earlier years were described on page 713 sought release from the sordid life to which he was exposed. Alcoholism was first noted at 12 years of age and lasted until his environment was improved, that is, until his placement in a foster home.

In spite of some serious symptoms, we wish to stress the transient nature of most of the psychopathic phenomena observed during adolescence. In general these were exhibited by the patients who also had problems relating to their home environment. The combination of the physical complications of diabetes mellitus, unsatisfactory social adjustment and a general feeling of inferiority was responsible for the transient psychopathic states. The following case is illustrative.

R. K. (case 20) contracted diabetes at the age of 11 years. The family consisted of her parents, a brother, a sister and a maternal uncle who boarded with them. The father was a waiter, who earned only a modest living. He was particularly sensitive about being dependent on his wife's brother for financial help. The nature of the father's work kept him away from home every night so that his influence on the rest of the family was minimal. This was accentuated even further by his passive temperament which was overwhelmed by his wife's dominance. The mother was a highly neurotic but fairly intelligent woman who struggled to maintain a neat and clean home despite a multiplicity of psychogenic complaints. These gave her reasons to attend numerous clinics. She was an oversolicitous, overprotective parent but she displayed undisguised favoritism toward the younger and normal daughter. This daughter, 5 years younger than the patient, was unusually "spoiled" by the mother, who openly proclaimed her "the least troublesome of the children." She was indulged to such an extent that even such privileges as staying up late, denied the patient, were granted the younger nondiabetic sister. The patient expressed deep resentment and jealousy toward his sister but was extremely fond of the younger brother. The boy, eight years younger than the patient, was a puny, sickly child who became asthmatic. With the appearance of this chronic ailment, he too had severe behavior disorders and, like the patient, attended the Behavior Clinic at Mount Sinai Hospital for some time. The patient "mothered" the boy, dressing and feeding him. She constantly accused her mother of neglecting him. In family quarrels the patient and her brother on the one side always opposed the mother and the sister on the other.

The development of diabetes apparently did not disturb the patient much, but the mother, in her solicitude, was overwhelmed by the care and attention required by the child. The mother constantly expressed anxiety and doubt as to her accuracy in weighing food. The tension of the home mounted progressively until at the end of the first year the mother wrote that she feared a "nervous break-

down." She described her daughter as given to frequent outbursts of temper and impudence, with constant threats of suicide. The two complained about each other continually when attending the clinic.

The patient entered high school at 13 years of age, expressing hopes of becoming a chemist. She was known as a "bookworm" and displayed a passionate interest in books on health. Her school work was satisfactory, but no close contacts were established with her classmates. Because of many symptoms of inadequate adjustment she was again referred to the Behavior Clinic. Soon after this she spent her first vacation at a summer camp for diabetic children and returned home "brighter and friendlier." The following year was noteworthy in that she developed close friendships with several other diabetic children attending the clinic, and, more important, formed attachments to her classmates. Her school work suffered, however, because of many absences due to recurrent infections of the upper respiratory tract. Her intelligence quotient at 16 was 114. She then expressed the desire to become a dietitian or a laboratory technician and seemed fascinated by hospital work. Her preoccupation with disease was indicated by the remarkably complete scrapbook which she maintained on matters pertaining to health and medical discoveries. As she developed an ever widening circle of friends of both sexes, her home life seemed happier. Her maturity was accompanied with increasing responsibility at home, with shopping, cleaning and generally helping her mother, who seemed more relaxed as the burden of diabetic care shifted to the patient. A more liberal prescription of the diet and the discarding of the practice of weighing the food further relieved both patient and mother. The mother began to respect her daughter's judgment and individuality.

A series of vocational interest tests was performed when the patient was 16½ years old. The total score showed a lack of ambition. She expressed keen interest only in nursing and bacteriology. The tests emphasized the narrow interests of the patient.

She completed the high school course but could not afford a college education, and her grades were not high enough to provide a scholarship. She felt unequal to the amount of study required in dietetic school or for laboratory training and realized that her ambitions were frustrated. At first she studied typewriting and shorthand in order to qualify for a clerical position, but soon economic pressure at home forced her to accept light manual factory work at \$12 a week. She was so unhappy in this, her first position, that she lost weight, became asthenic and was sent to a convalescent home. On her return she applied for a civil service position and in 1942 became the first applicant with diabetes to be accepted by the Civil Service Commission of the United States. She was placed in the Brooklyn Navy Yard offices, where she seemed quite happy for almost a year. At that time she was offered a position at a higher salary with a business firm, where she has remained.

She had met a young German refugee, who seemed fond of her. They saw each other regularly until he was inducted into the army, and even then their meetings were still fairly frequent. During this period there had been no mention of diabetes or of marriage. R. K. was happy at work and gained weight, and her diabetes seemed less troublesome. She maintained a daily correspondence with her friend while he was overseas. She visited his parents weekly and enjoyed their company. After several months she began to display anxiety over the concealment of the diabetes. She had refrained from mentioning it to the young soldier before he had gone overseas because she felt that its presentation "would be easier in writing." After considerable delay and self reproach she

informed him that she had diabetes. He replied that the condition "made no difference" in his feelings toward her. Although this answer pleased her she felt guilty over the concealment. She expressed doubts as to the possibility of marriage, and she considered interruption of their correspondence. As her unhappiness increased, her depression deepened; she lost weight, slept poorly and was subject to "crying spells." She presented a picture of complete discouragement. Psychiatric assistance helped overcome her feeling of insecurity, and the depression vanished as prospects of her fiancé's early return seemed promising. At the present time she is happy at work, eagerly anticipating her forthcoming marriage.

INTELLIGENCE TESTS

Because the literature⁹ contains conflicting statements concerning the intelligence of diabetic children, we attempted to obtain such data from our group.

Revised Stanford-Binet-Simon intelligence tests and vocational tests were given to 24 patients. The results of the tests are presented in table 2. Of the 24 patients, 20 had an intelligence quotient of 90 or

TABLE 2.—*Range of Intelligence Quotients of Twenty-Four Clinic Patients*

Intelligence Quotients	Patients	Total
70 - 80.....	2	4
80 - 90.....	2	
90 - 100.....	6	8 average
100 - 110.....	2	
110 - 120.....	4	12
120 - 130.....	4	
130 - 140.....	4	
	24	

more. Only 4 quotients fell below this figure. The mental level of the diabetic children and adolescents was similar to that of nondiabetic patients of the same ages who have been tested at our hospital.¹⁰ These results demonstrated that young diabetic patients were neither "brighter" nor "duller" than normal.

None of the reported studies of the intelligence of diabetic children included reexaminations made after an interval of time. We investigated this aspect by repeating the Stanford-Binet test with 10 patients after an interval of several years. The intelligence quotients of 8 of them showed no significant alteration. There was a rise in one and a fall in another.

9. (a) Brown, G. D., and Thompson, W. H.: The Diabetic Child, *Am. J. Dis. Child.* 59:238 (Feb.) 1940. (b) Grishaw, W. H.; West, H. F., and Smith, B.: Juvenile Diabetes Mellitus, *Arch. Int. Med.* 64:787 (Oct.) 1939. (c) McGavin and others.² (d) Joslin and others,⁷ p. 679.

10. Davis, R.: Personal communication to the authors.

ADJUSTMENTS

1. *Method of Evaluation.*—We have attempted to correlate a number of facts and have used the term "adjustment" to summarize our impressions of the reaction of the child to his diabetes, to his family and to society. Each child's adjustment was graded "excellent," "good," "fair" or "poor." This judgment was based on our personal impressions over many years of observation. Temperament and achievement were also considered in this evaluation. We considered "excellent" such patients as were happy at home, at school and at work, whose diabetes did not interfere with their daily life and who were able to live normally. The others were graded in relation to this superior group. Our tabulations were based on the status of the patients on Dec. 1, 1945. In general the patients with higher intelligence quotients made more satisfactory adjustments.

2. *Economic Status.*—Table 3 shows that the adjustment of private patients was "excellent" or "good" in contrast to that of the clinic or poorer group, in which fewer were well adjusted. We attempted to reclassify periodically the adjustments which our patients made.

TABLE 3.—*Adjustment of Clinic Versus Private Patients*

Adjustment	Clinic	Private	Total
Excellent.....	4	2	6
Good.....	9	4	13
Fair.....	11	2	13
Poor.....	10	1	11
Total.....	34	9	43

However, we found that the individual variations did not lend themselves to statistical evaluation. Some of the factors, such as maturity and marriage, usually improved the psychologic attitude, and, in contrast, blindness or other chronic complications naturally made it worse.

3. *Home Environment.*—Home environment included the economic status, harmony or lack of it among the members of the family and their reaction to the patient. When the home environment was excellent or good as it was in 23 instances (table 4), there were no poorly adjusted children, 16 being considered to show excellent or good and 7 fair adjustment. On the other hand, only 3 of the 20 from fair or poor homes could be considered well adjusted, the rest manifesting fair or poor adjustment. Socioeconomic factors were significant in influencing the behavior of juvenile diabetic patients, and were more important than for nondiabetic patients.

4. *Scholastic Achievement.*—It was noted that there were 18 diabetic patients whose scholastic achievement was good; 12 of these were doing fairly well, and 6 showed what was considered excellent achieve-

ment (table 5). Of these 18, 15 came from the well adjusted group as might be expected. On the other hand, of the 25 children with poor scholastic records, only 4 came from the well adjusted group; 11 came from the group with fair adjustment and 10 from the badly adjusted group. It is apparent therefore that scholastic achievement paralleled adjustment of the child and that both were directly related to the type of home and the economic status. Most of the children were able to attend school regularly and completed their studies satisfactorily.

TABLE 4.—*Adjustment of Patients Related to Home Environment*

Adjustment	Home Environment			
	Excellent	Good	Fair	Poor
Excellent.....	4	2
Good.....	3	7	1	2
Fair.....	..	7	3	3
Poor.....	3	8
Total.....	7	16	7	13

There were some who fell behind because of frequent illness, often the result of a diabetic complication. On the other hand, others who had no interest or capacity for school welcomed any opportunity to avoid it. For example, although the main diabetic clinic session at the hospital was held on Saturday mornings so as not to interfere with school attendance, these patients deliberately chose to come to the clinic on week days.

TABLE 5.—*Adjustment of Patients Related to Scholastic Achievement*

Adjustment	Scholastic Achievement			
	Excellent	Good	Fair	Poor
Excellent.....	5	1
Good.....	1	8	4	..
Fair.....	..	2	5	6
Poor.....	..	1	3	7
Total.....	6	12	12	13

5. *Manual Achievement.*—In general, tests for manual dexterity gave results similar to those obtained with the Binet-Simon test. There were, however, some exceptional instances in which poor mental capacity was accompanied with remarkable manual dexterity.

M. B. (case 4), who by the Stanford-Binet test had an intelligence quotient of 72 at the age of 16 (mental age of 10), displayed unusual manual ability in mechanical assembly and paper folding. M. P. (case 31) had no intellectual ambition whatsoever but willingly accepted unremunerative heavy manual work.

These cases illustrate a fact well known to vocational guidance advisers, namely, that patients with dull mentality do not find monotonous work

irksome. The development of special skills was encouraged in such children by sending them to vocational high schools.

6. *Occupations*.—Forty-two per cent of the patients reported on by Eisele¹¹ from the clinic of the New England Deaconess Hospital were college graduates. Our patients were younger; many were still attending high school. Only 4 of our patients have completed college. The others because of their economic status were forced to enter industry in order to support their families, after completing high school.

None of the 43 patients has achieved anything approaching outstanding success. However, the group is still young and is handicapped economically and socially. During adolescence there was a striking tendency to seek employment in food industries. Most of them were employed as soda fountain clerks, sandwich makers, ice cream and orangeade venders, candy salesmen and butchers' helpers. Some of the girls expressed the desire to become nurses or dietitians, yet none actually did so. As the patients became older and acquired skills, most of the girls became clerks and saleswomen and the boys chose light mechanical or clerical work. A tendency to change positions frequently, a characteristic of youth, was noted. Some patients avoided applying for positions which required physical examinations and, if eager for a certain job, resorted to subterfuge for the urinalysis. Many of the patients felt that public knowledge of their being diabetic might jeopardize their business opportunities. However, even after employment had been obtained, our patients were fearful that their illness become known.

Examples of concealment included: the secretary of a newspaper executive, M. J. (case 17); a business machine operator in a Wall Street firm, M. T. (case 42); a salesgirl in a department store, G. K. (case 19), and a shipping clerk in a clothing firm, H. C. (case 5).

S. S. (case 36), another salesgirl, became panicky when she recognized the physician who was treating her as he entered the store in which she was employed. Glancing fearfully at the other employees, she whispered the following greeting, "Please forgive me for not calling you 'Doctor' here; I don't want the others to know I'm sick."

It is commendable to note that the Federal government permits applicants with diabetes to qualify for civil service positions. G. S. (case 37) and R. K. (case 20) held such positions. Further extension of this progressive step would be of great value to the large numbers of diabetic persons seeking employment today.

MARRIAGES AND BIRTHS

The fears and anxieties regarding marriage which were expressed during adolescence were accentuated as adulthood approached. Nine

11. Eisele, H. E.: The Juvenile Diabetic Patient Surviving Twenty Years, *J. A. M. A.* **120**:188 (Sept. 19) 1942.

male and 5 female patients of our series married (table 6). The attainment of marriage seemed more difficult for the girls. As 1 of our patients, S. S. (case 36), expressed it, "a girl with diabetes has two strikes against her when it comes to getting married." This girl was engaged to be married on three occasions, yet each suitor revoked his proposal on learning of her diabetes. Her growing cynicism was expressed by her statement, "I will not tell the next one until I have the wedding ring on my finger." This unmarried girl unfortunately became pregnant and died after a therapeutic abortion. Although the girls desired marriage, more so than the boys, many of them felt or

TABLE 6.—*Marriages and Births*

Patient	Case	Adjust- ment	Year of Mar- riage	Births	Success of Marriage	Type of Work of Mate	Personality of Mate
Female patients							
S. G.	10	Fair	1937	1 mis. 1 still.	Good	Mechanic	Understanding
E. H.	11	Fair	1936	None	Good	Electrician	Average
M. K.	18	Excellent	1934	1 mis. 1 still.	Good	Optical lens worker	Intelligent
E. S.	38	Good	1941	None	Separated	Civil service	Intelligent
J. Z.	43	Poor	1939	1 child 1 mis.	Poor	Salesman	Unintelligent, unsympathetic
Male patients							
H. C.	5	Good	1943	None	Good	Housewife	Very young, immature
N. G.	7	Fair	1944	None	Poor (separated)	Housewife	Intelligent, solicitous
G. H.	14	Good	1940	None	Good	Secretarial	Superior, understanding
A. N.	30	Good	1942	1 child	Good	Housewife	Understanding, helpful
G. S.	37	Excellent	1945	None	Not certain (too recent)	Housewife	Sympathetic
M. T.	42	Good	1943	1 child	Good	Housewife	Intelligent
J. M.	29	Excellent	1945	None	Not certain (too recent)	Housewife	Fairly intelligent
H. I.	16	Good	1945	None	Not certain (too recent)	Nurse	Sympathetic, intelligent
E. L.	26	Fair	1944	1 child	Poor (separated)	Unknown	Unknown

expressed a distinct apprehension about it. Their fears were concerned with the burdens of diet and insulin as well as the possibility of transmitting diabetes to their offspring. This fear was an extremely difficult one to overcome. Patients faced an additional problem because of a lack of intelligent understanding, sympathy and cooperation on the part of parents-in-law, who frequently resented the fact that their nondiabetic child had assumed a lifelong burden. Thirteen of the diabetic patients married into families that were not diabetic as far as is known. The fourteenth patient was able to marry only because his fiancée understood and accepted his problem, her own father being diabetic. However,

despite drawbacks, we have been gratified that most of the marriages thus far seem to have been reasonably happy ones. All but 2 of the married patients were in the well adjusted or moderately well adjusted group before marriage. Two male patients, N. G. (case 7) and E. L. (case 26), and 1 female (E. L. case 38) became separated within two years after marriage.

With respect to child bearing, the experience of this group has not been gratifying. Only one living child was born to 3 female patients, each of whom became pregnant twice. Thus, of the six pregnancies, five terminated in stillbirths and miscarriages. Two other female patients have not as yet become pregnant. The 2 patients who failed to bear living children were greatly depressed by their misfortune. Fortunately, both were able to adopt infants through the aid of social agencies.

Of the 9 male patients 3 became fathers; the wives of 5 have not become pregnant as yet, and 1 patient has been reluctant to assume the responsibility of parenthood because he has both diabetes and tuberculosis.

The disappointing record of childbirths of this group can be explained by a number of factors. The long duration of diabetes (average fifteen years) and the onset of degenerative changes are important general causes of the high fetal and neonatal mortality. Because of the lack of an obstetric department in our hospital the patients were transferred to other hospitals with interruption of continuity of the diabetic regimen.

COMMENT

Previous publications in our opinion have inadequately presented the influence of the disease on the behavior of young diabetic patients. Joslin,¹² for example, devoted a single paragraph to the psychologic problems of the diabetic child and a few sentences to their mental adjustments. Duncan¹³ likewise discussed the subject briefly. Others¹⁴ did not mention it at all or limited their studies to a few years.¹⁵ Loughlin and Mosenthal³ made a report on the personalities of diabetic children at a summer camp (Camp Nyda, at Burlingham, N. Y.) during a brief vacation.

It is obvious that short term observations such as these give only a partial view of an ever changing panorama. Trite expressions such as "diabetic children are unusually bright" are incorrect when one

12. Joslin and others,⁷ p. 690.

13. Duncan, G. G.: *Diseases of Metabolism*, Philadelphia, W. B. Saunders Company, 1942.

14. (a) Wilder, R. M.: *Clinical Diabetes Mellitus and Hyperinsulinism*, Philadelphia, W. B. Saunders Company, 1941. (b) Wirtschafter, Z. T., and Korenberg, M.: *Diabetes Mellitus*, Baltimore, Williams & Wilkins Company, 1942.

15. McGavin and others.² Brown and Thompson.^{9a} Grishaw and others.^{9b}

studies these patients carefully over long periods. One of the children observed briefly by Loughlin and Mosenthal was classified as a "normal, ideal boy," but within two years he exhibited a psychopathic personality for which he was treated at Bellevue Hospital.

The present report and also those of Eisele¹¹ and Rosenbusch¹⁶ differ from those just mentioned in that the psychologic and personality reactions of diabetic children have been carefully followed through years of childhood, adolescence and early adult life. Rosenbusch's studies are most thorough. He followed a group of 88 children for as long as twenty years.

With the exception of Brown and Thompson^{9a} the authors cited concurred in the opinion that personality changes and maladjustments were to be expected in the life of the diabetic child. Brown and Thompson found "no characteristic abnormalities in personalities." Their analysis was based on the initial examination and follow-up reports from schools and parents. It seems likely that subsequent personal examinations of their patients eventually would have revealed abnormalities not present at the earlier examination. Rosenbusch¹⁶ found "psychopathological behavior in a number of patients."

McGavin and coworkers² stated that children who had intelligence tests were neither significantly brighter nor duller than nondiabetic children. Brown and Thompson found that their patients were distributed normally with regard to intelligence. Brown and Thompson further explained Joslin's^{9d} report of higher intelligence quotients among his patients on the basis of a selection from an upper socioeconomic group. Rosenbusch¹⁶ also found average intelligence among his patients. Grishaw and others^{9b} found a higher intelligence quotient than normal in 62 "unselected" patients. We could find no significant difference in the intelligence as determined by the Stanford-Binet test in 24 diabetic patients attending the outpatient clinic as compared with a similar group of nondiabetic patients tested by the same psychologist.

This survey would be incomplete were we not to call attention to the fact that diabetes is similar to other chronic illnesses in its effect on the psyche. Just as a hunchback or a cripple is always aware of his deformity, so the diabetic child is always conscious of his condition. He cannot escape the daily injection and is constantly reminded of his affliction by the discomfort produced by the needle as well as by the restriction in diet. Furthermore, in many persons each dose injected is associated with the fear of a possible hypoglycemic reaction. When behavior disorders arise in homes where there is conflict and insecurity, the reaction is the more serious. Conversely, an ideal adjustment is possible if there is understanding, harmony and security in the home.

16. Rosenbusch, H.: Prognose und Spätkomplikationen des Diabetes Mellitus im Kindesalter, *Ann. pædiat.* **164**:225 and 281, 1945; **165**:12, 1945.

SUMMARY

The problems which arose in 43 young diabetic patients from childhood through adolescence to maturity have been analyzed. No patient who had not been observed for at least ten years was included in this report.

The type of home, its economic security and the contacts at school and in social life, all had especial influence on the reaction of the diabetic child to his disease.

Specific problems of childhood became less disturbing with the onset of maturity. During adolescence, problems relating to vocation and marriage appeared. Maturity usually brought about improvement in behavior, with the desire for independence being its outstanding characteristic. Marriage for the young diabetic person was difficult, especially for the young women. However, most of the marriages have been happy ones.

The specific effects of diabetes on behavior were found to be unrelated to the age of onset, the duration or the severity of the disease.

Diabetic regimentation, while necessary, at first, produced behavior difficulties.

The immediate and the more remote or cumulative effects of hypoglycemia on the brain were considered to be potentially serious.

Psychopathic behavior in a serious form was exhibited in 3 patients; other minor behavior disturbances were frequent.

The results of intelligence tests were not significantly different from those of tests given to a similar socioeconomic nondiabetic group. No demonstrable change was noted in those patients who were retested. The patients in the better economic group and with better home environment had higher intelligence quotients and made more satisfactory adjustments to diabetes.

CONCLUSION

Diabetes mellitus produces many psychologic problems which may result in abnormal behavior throughout childhood, adolescence and adult life.

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Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

FRANK W. REYNOLDS, M.D.

AND

JOSEPH EARLE MOORE, M.D.

BALTIMORE

(Continued from Page 625)

PENICILLIN THERAPY

Only in England, where penicillin was discovered, and in the United States, where its usefulness in syphilis first was demonstrated, has penicillin been used extensively in the treatment of syphilis. In other countries, either penicillin has been unavailable or its use has been restricted to more acutely lethal infections. Consequently, information concerning the treatment of syphilis with penicillin thus far has appeared only in British and American journals. Summaries of recent developments without original observation have recently appeared in the Latin-American,⁹³ French⁹⁴ and Indian⁹⁵ literature.

In the United States, a nationwide study of the effect of penicillin in the treatment of syphilis was begun Sept. 1, 1943, under the auspices of the Committee on Medical Research. On Jan. 1, 1946, the financing and general supervision of the project were taken over by the National Institute of Health, United States Public Health Service. Prior to this date the study was directed by the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council, and subsequently by the Syphilis Study Section of the National Institute of Health. Participating in the study are forty-one clinics and seven laboratories of experimental syphilis. As a result of their collective and cooperative efforts, an enormous amount of factual data has been compiled. Few if any new therapeutic agents have been studied so extensively in such a brief period as has penicillin in its relation to syphilotherapy.

93. Castanedo y Pardo, C.: *Penicillina y sífilis*, Rev. sif., leprol. y dermat. **2**: 101 (June) 1945. Pardo Castello, V.; Ferrer, I., and Castanedo, C.: *La penicillina en tratamiento de la sífilis*, Rev. sif., leprol. y dermat. **3**:5 (Jan.) 1946.

94. Marshall, J.: *Le traitement de la syphilis par la pénicilline*, Ann. de dermat. et syph. **9-10**:228 (Sept.-Oct.) 1945. de Gennes, L., and Cournot, L.: *Le traitement de la syphilis par la pénicilline*, Presse méd. **24**:344 (May 25) 1946.

95. Nair, V. G.: *Penicillin in the Treatment of Venereal Diseases*, Indian J. Ven. Dis. **11**:69 (Oct.-Dec.) 1945.

The Chemistry of Penicillin and the Pharmacology of the Several Penicillin Fractions.

During World War II, many laboratories in the United States and Great Britain participated in an extensive study of the chemistry of penicillin. Censorship of the project was carefully maintained, and the secrecy has proved to have been a double-edged sword. It had the somewhat dubious virtue of withholding information that might conceivably have given "aid and comfort to the enemy." It also had the disadvantage of delaying scientific progress by withholding important knowledge from competent investigators.

Be that as it may, some time after the cessation of hostilities medical knowledge formerly considered "secret" was gradually released. There recently appeared a statement issued jointly by the American Committee on Medical Research⁹⁶ and the British Medical Research Council⁹⁷ concerning the chemistry of penicillin.

The details of this summary are more relevant to the work of the research chemist than to the medical practitioner. It is of interest, however, that penicillin is thought to have the empiric formula $C_9H_{11}O_4SN_2R$, the differences between various penicillin species depending on a substituent group in the molecule. (In penicillin G, this substituent represents a benzyl group; in penicillin F, *n*-amyl; in penicillin X, *p*-hydroxy-benzyl, and in penicillin K, *n*-heptyl.) Each species can be converted into various metallic salts or esters. The precise structural formula of penicillin is still undetermined, however, and its synthesis has not yet been formally announced.

As information regarding the various penicillin species increased and as data relative to the chemistry of penicillin gradually became available, there was accumulating evidence that changes were occurring in the character of the commercial product. Physicians who had been using penicillin for various infections became aware of the increasing doses required to accomplish the therapeutic results they had become accustomed to expect. This decline in the effectiveness of commercial penicillin soon was manifested by increasingly high relapse rates in early syphilis, and it was in the cooperative study of this condition that the changing character of penicillin first was suggested and quantitated.

The details of the fascinating story, which reads like detective fiction, of how this information was uncovered and of how the evidence was logically analyzed step by step, have been published in a joint state-

96. Chemistry of Penicillin, Committee on Medical Research, Washington, and Medical Research Council, London, *Science* **102**:627 (Dec. 21) 1945.

97. Chemistry of Penicillin, Medical Research Council, London, and Committee on Medical Research, Washington, *Nature*, London **156**:766 (Dec. 29) 1945.

ment⁹⁸ by the Committee on Medical Research, the United States Public Health Service and the Food and Drug Administration.

It was shown that the results of penicillin therapy in early syphilis have been distinctly less favorable since May 1944 than prior to that date, almost surely because there have occurred, as a result of certain changes in the manufacturing processes designed to increase the yield and the "purity" of the product, alterations in the character of commercial penicillin. These changes were in two directions: (1) a change in relative quantities of penicillin species, with a probable substantial decrease in the amount of penicillin G and an equal compensatory increase in the amounts of penicillins F and K, especially the latter, and (2) the increasing purity of penicillin in terms of units per milligram and a corresponding decrease of impurities that possibly have therapeutic activity. All the recent information indicates that the first of these two changes is by far the more important.

It has been suggested⁹⁹ that crystalline forms of penicillin may be less effective against syphilis than partially purified preparations. As reported by Williamson and Lourie,¹⁰⁰ however, so far as therapeutic trials against *Borrelia recurrentis* infections in mice may be an index of the true situation, there is no superiority of partially purified preparations over crystalline penicillin G. Penicillin X was found less efficacious than penicillin G in the treatment of these spirochetal infections in mice.

The results of studies in which the various penicillin fractions are compared in respect to their activity in vitro or in vivo must be interpreted with due regard to whether the comparison is on an Oxford unit for unit basis or in gravimetric terms, involving comparable weights.

Libby and Holmberg,¹⁰¹ for example, have found evidence that, milligram for milligram, penicillin G is more efficacious in vitro against *Staphylococcus aureus* and *Bacillus subtilis* and that the X fraction is superior against pneumococci, streptococci and *Escherichia coli*.

98. The Changing Character of Commercial Penicillin, with Suggestions as to the Use of Penicillin in Syphilis, Committee on Medical Research, the United States Public Health Service and the Food and Drug Administration, J. A. M. A. **131**:271 (May 25) 1946.

99. Dunham, W. B., and Rake, G.: The Relative Activity of Partially Purified Penicillin and of Crystalline Penicillin G on *Treponema Pallidum*, Am. J. Syph., Gonorr. & Ven. Dis. **29**:214 (March) 1945.

100. Williamson, J., and Lourie, E. M.: Therapeutic Action of Different Penicillins on *Spirochaeta Recurrentis* Infections in Mice, Brit. M. J. **1**:828 (June 1) 1946.

101. Libby, R. L., and Holmberg, N. L.: The Activity of Penicillins G and X in Vitro, Science **102**:303 (Sept. 21) 1945.

Ory, Meads and Finland¹⁰² report that, when tested with preparations containing 65 per cent or more of penicillin X and with commercial lots which were almost entirely penicillin G, hemolytic streptococci, gonococci and meningococci were (in terms of Oxford units) from two to eight times more sensitive to penicillin X, pneumococci and *Streptococcus viridans* were twice as sensitive to penicillin X and most staphylococci were equally sensitive to the two kinds of penicillin. Levels of penicillin activity in the serum were higher and sustained longer after intramuscular injections of penicillin X than after injections of the same number of units of "regular" penicillin.

A preliminary clinical trial indicated to the authors that:

Penicillin X is nontoxic and at least as effective as regular penicillin in the same doses in cases of pneumonia and probably more effective in gonococcal infections. Further trials with the use of smaller doses and longer intervals are necessary in order to establish the therapeutic superiority of penicillin X.

In an in vivo study, Richardson and his associates¹⁰³ have compared the spirocheticidal activity against *Clostridium oedematiens* of four preparations of penicillin varying in degree of purity and containing varying proportions of penicillin G and other penicillins. On the basis of dosage in Oxford units, no differences were noted among the four samples, regardless of the method of administration.

In the treatment of experimental syphilis, penicillin K has been far less efficient¹⁰⁴ than other penicillin compounds. This low therapeutic activity of penicillin K has been found by Eagle and Musselman¹⁰⁵ to be due to the fact that penicillin K disappears from the blood more rapidly than do the other penicillins. One hour after the injection into rabbits or human beings of penicillins G, F, X and K, blood levels of penicillin K were one fourth to one eleventh of those observed with the other penicillins, and penicillin K persisted at demonstrable levels for relatively short periods. The recovery of penicillin K in the urine averaged only 30 to 35 per cent, whereas the average recovery of penicillins G, F and X was 74 per cent in rabbits and 91 per cent in human beings.

102. Ory, E. M.; Meads, M., and Finland, M.: Penicillin X: Comparison with Penicillin G with Respect to Sensitivity of Pathogenic Organisms and Serum Levels, *J. A. M. A.* **129**:257 (Sept. 22) 1945.

103. Richardson, A. P.; Walker, H. A.; Loeb, P., and Miller, I.: The Experimental Basis for the Quantitative Chemotherapy of *B. Novyi* in Mice with a Comparison of Action of Penicillin and Dichlorophenarsine Hydrochloride, *J. Pharmacol. & Exper. Therap.* **85**:23 (Sept.) 1945.

104. Chesney, A. M.: Unpublished data. Mahoney, J. F., and Arnold, R. C.: Unpublished data.

105. Eagle, H., and Musselman, A.: The Low Therapeutic Activity of Penicillin K Relative to That of Penicillins, F, G, and X, and Its Pharmacological Basis, *Science* **103**:618 (May 17) 1946.

Coghill, Osterberg and Hazel¹⁰⁶ have confirmed this important observation. In their study, the preparations used were analytically pure crystalline penicillins G, X and K. Twenty-five thousand units were injected intravenously and concentrations of penicillin in the blood and urine determined at suitable intervals. The duration of penicillin blood levels of at least 0.03 unit per milliliter for each of the penicillins was G, two to two and one-half hours; X, four to four and one-half hours, and K, one-half to three-fourths hour. The inefficient action of penicillin K as compared with the action of penicillins G and X is explained by comparison of the urinary excretions. During the first two hours, 83 per cent of penicillin G was excreted, 78 per cent of penicillin X and only 28 per cent of penicillin K.

These data indicate that penicillins G, F and X are of sufficient stability in the human body that the maintenance of adequate blood levels is conditioned almost entirely by the amount lost by excretion in the urine and that penicillin K is inactivated in the body more rapidly and to a greater extent than penicillins G, F and X. Of considerable practical importance is the fact that, because of its low therapeutic value, the amount of penicillin K in commercial penicillin should be kept minimal.

It should be stressed, in view of the publication in the lay press of a sensationalized and inaccurately presented article,¹⁰⁷ that the penicillin manufacturers are aware of the situation, are cooperating in the study of penicillin fractions and are taking practical steps to correct the identifiable difficulties in production.

Mode of Action.

The precise way in which penicillin acts to destroy *T. pallidum* is still unknown. Frazier and Frieden,¹⁰⁸ who have reviewed the published information pertaining to the mechanism of its action, state the belief that penicillin acts chiefly as a bactericidal, and therefore presumably spirocheticidal, agent. Data pointing to a spirochetistatic action of penicillin are not lacking, however, and the authors themselves report changes in the structure of spirochetes obtained from patients under treatment with penicillin. In 5 patients, it was observed that as treatment progressed there was a relative increase in the number of long forms of the spirochete. The increase was progressive within limits until organisms no longer could be found in dark field preparations. The long forms were, in general, less motile than short

106. Coghill, R. D.; Osterberg, A. E., and Hazel, G. R.: The Relative Effectiveness of Pure Penicillins G, X and K, *Science* **103**:709 (June 14) 1946.

107. Deutsch, A.: Plan National Roundup of Syphilis Victims Endangered by Treatment with Penicillin K, *PM Daily* **6**:13 (April 22) 1946.

108. Frazier, C. N., and Frieden, E. J.: Action of Penicillin, Especially on *Treponema Pallidum*, *J. A. M. A.* **130**:677 (March 16) 1946.

forms and occasionally were angulated at the middle. In the light of this finding, the writers speculate as to whether the elongation of spirochetes observed in these cases "may not be an indication of excessive growth and delayed cellular division."

While penicillin-resistant strains of bacteria such as the staphylococcus, pneumococcus, streptococcus and gonococcus can be produced in vitro, little is known about the adaptability of spirochetal organisms to this antibiotic agent. To elucidate this problem, Tsun and Frazier¹⁰⁹ have made in vitro studies on the adaptability of the Reiter strain of cultured spirochetes to increasing amounts of penicillin. In attempting to increase the resistance to penicillin of these spirochetes, the authors were faced with the difficulty of overcoming the slow rate of growth. This long period of growth resulted in some deterioration of the antibiotic agent at the temperature of incubation (37 C.). Even with these unfavorable factors, they were able to demonstrate that the Reiter strain of so-called *T. pallidum* did not develop an increased tolerance to penicillin after being subjected to fifteen consecutive passages through mediums containing penicillin. The effect of penicillin on the spirochetes appeared to involve an inhibition of cellular division, with resulting elongation and early death of the spirochetes observed in fresh cultures containing penicillin. Electron microscopic studies revealed that the long forms which developed after exposure to penicillin had lost their flagella.

Thus, although bacteria have been made resistant to penicillin in the test tube, there is yet no evidence that spirochetal organisms become penicillin fast. Thus far at least, penicillin resistance has not been a problem in syphilis. As more definitive information is lacking on the optimum time-dose relationships involved, it is, of course, difficult to define precisely what constitutes "penicillin resistance." The report of Tyson¹¹⁰ is entirely unconvincing.

Tainter¹¹¹ summarized the problems of bacterial "fastness" to sulfonamide drugs and to penicillin. He states the belief that there is no indication that the mechanism involved in the development of penicillin resistance is the same as that in the case of resistance to the sulfonamide compounds, particularly if the importance of para-aminobenzoic acid is granted. Penicillin apparently blocks the growth of organisms by interfering with the process of division. It has only

109. Tsun, T., and Frazier, C. N.: Penicillin Sensitivity and Morphology of the Reiter Strain of *Treponema Pallidum* After Cultivation in Media Containing Penicillin, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:205 (May) 1946.

110. Tyson, W. G.: Early Syphilis Resistant to Treatment with Penicillin, *J. Invest. Dermat.* **6**:279 (Oct.) 1945.

111. Tainter, M. L.: A Summary of the Problems of Sulfa and Penicillin Fastness, *New York State J. Med.* **45**:2509 (Dec. 1) 1945.

weak action on spores and little effect on organisms in the resting phase. In some respects, penicillin behaves as an enzyme rather than as a compound which is used up in producing its physiologic effect. The question of how micro-organisms become resistant to the action of penicillin has as yet not been satisfactorily answered. The author critically analyzes the proposed explanations for the phenomenon. The prevention of the development of penicillin-fast strains of micro-organisms is important if penicillin is to continue as highly successful as it is at present. It is suggested that the use of effective doses from the onset of treatment is desirable. Ineffectual dosages, especially those which result from self medication, are deplored.

Dosage.

Raiziss' ¹¹² experiments with a limited number of animals indicate that in rabbits syphilitic infections apparently are cured by 40,000 Oxford units of penicillin per kilogram of body weight given over a period of eight days, whether in aqueous solution or in oil suspension. Translated into a treatment schedule for human beings of 60 Kg., the total dose for the patient would be 2,400,000 units. Since, however, larger doses of penicillin appeared to cause more rapid healing of lesions and probably to compensate for differences between human and rabbit syphilis, the author recommends that the "total treatment" for a patient weighing 60 Kg. be 4,800,000 units of penicillin.

Methods of Administration.

Turton ¹¹³ has found that continuous intramuscular infusion is a practicable method of administering penicillin in a busy hospital ward. Hirsh and Dowling ¹¹⁴ also conclude that continuous intramuscular infusion is the method of choice for the parenteral administration of penicillin. These authors employed continuous intramuscular administration of penicillin in 110 patients, without deleterious effects except for mild to moderate pain in 6 patients. Pain usually could be prevented by changing the site of injection occasionally and by the addition of procaine hydrochloride to the infusion.

In maintaining consistently high serum levels of penicillin, Loewe and his associates ¹¹⁵ found the continuous intravenous drip superior

112. Raiziss, G. W.: The Effect of Penicillin in Experimental Rabbit Syphilis, *Science* **102**:329 (Sept. 28) 1945.

113. Turton, E. C.: Administration of Penicillin by Intramuscular Infusion, *Brit. M. J.* **2**:283 (Sept. 1) 1945.

114. Hirsh, H. L., and Dowling, H. F.: Observations on the Continuous Intramuscular Method of Administering Penicillin, *Am. J. M. Sc.* **210**:435 (Oct.) 1945.

115. Loewe, L.; Rosenblatt, P.; Russell, M., and Altire-Werber, E.: The Superiority of the Continuous Intravenous Drip for the Maintenance of Effectual

to fractional intramuscular or continuous intramuscular methods of injection.

Ory and his co-workers¹¹⁶ also determined penicillin levels in blood serum following administration by a variety of routes. In contradistinction to the aforementioned reports, these workers found that serum levels following continuous intravenous or continuous intramuscular administration usually were no higher than those following intermittent intramuscular injection of comparable doses at two hour intervals, provided the fluid intake was restricted. With both continuous intravenous and continuous intramuscular infusions, serum levels were fairly constant in one person but variable among different patients on the same dosage.

On the hypothesis that continuous levels of penicillin in the blood stream may not be necessary in the treatment of syphilis and hoping to evolve a time-dose relationship for administering sodium penicillin suitable for ambulatory patients, two groups of English workers have utilized schemes of intermittent penicillin therapy.

Lourie and his associates¹¹⁷ treated 17 patients with early syphilis by the administration of three doses of 600,000 units of sodium penicillin at hourly intervals, given on five successive days. In each case, infectious lesions disappeared and seronegativity was attained.

Lloyd-Jones, Allen and Donaldson¹¹⁸ treated 215 patients with early syphilis by single daily injections of sodium penicillin. Individual injections were of 300,000 or 500,000 units and the duration of therapy from five to fifteen days. In one series, penicillin was given intravenously; in another, the intramuscular route was utilized. The immediate response was similar to other forms of penicillin therapy: spirochetes disappeared, the lesions healed and serologic reactions became negative. When daily injections of 300,000 units were given intravenously, an infectious relapse rate of 9 per cent was observed. With the same amounts given intramuscularly, 5.5 per cent of the patients had early relapses. When the daily injections were each of 500,000 units, the relapse rate was lower. Thirty additional patients were treated with 3,000,000 to 5,000,000 units of penicillin administered as massive

Serum Levels of Penicillin: Comparative Studies with Particular Reference to Fractional and Continuous Intramuscular Administration, *J. Lab. & Clin. Med.* **30**:730 (Sept.) 1945.

116. Ory, E. M.; Meads, M.; Brown, B.; Wilcox, C., and Finland, M.: Penicillin Levels in Serum and in Some Body Fluids During Systemic and Local Therapy, *J. Lab. & Clin. Med.* **30**:809 (Oct.) 1945.

117. Lourie, E. M.; Ross, A. O. F.; Nelson, R. B.; Collier, H. O. J., and Robinson, D. T.: Ambulatory Treatment of Early Syphilis with Penicillin, *Lancet* **2**:696 (Dec. 1) 1945.

118. Lloyd-Jones, T. R.; Allen, S. J., and Donaldson, E. M.: Out-Patient Treatment of Early Syphilis with Penicillin, *Brit. M. J.* **1**:567 (April 13) 1946.

single doses, repeated daily for from one to five days. With these time-foreshortened schedules, relapse rates were between 50 and 100 per cent.

Intrathecal Administration.—It has been demonstrated repeatedly that penicillin does not penetrate into the cerebrospinal fluid in appreciable amounts after intramuscular or intravenous injection. McDermott and Nelson,¹¹⁹ using dilution technics of bioassay, were unable to demonstrate penicillin in spinal fluids obtained from 70 patients who had received intramuscular injections of doses as high as 500,000 Oxford units. At concentrations of 0.078 to 1.25 units of penicillin per cubic centimeter of blood serum, penicillin was found to diffuse through artificial membranes in vitro and into ascitic fluid in vivo. Thus the failure of penicillin to appear in the cerebrospinal fluid seemed not to be because it is bound significantly to nondiffusible elements in serum.

Kaplan and his associates¹²⁰ report that examination of spinal fluids of 12 neurosyphilitic patients from ten to one hundred and fifty minutes following intramuscular administration did not reveal the presence of penicillin (within the limits of the test employed, i. e., less than 0.125 unit per cubic centimeter).

Dumoff-Stanley and her co-workers¹²¹ also conclude that the systemic administration of penicillin in the doses commonly employed does not consistently yield measurable concentrations of the drug in the cerebrospinal fluid.

With penicillin therapy in massive doses by continuous intravenous drip (10,000,000 to 25,000,000 units given over a period of twenty-four hours), Schwemlein and his associates¹²² were able to demonstrate measurable concentrations in the cerebrospinal fluids of 126 of their 162 patients (77.7 per cent). There was a direct relationship between the total dosage and the observed levels of penicillin in the spinal fluid but no clear correlation between blood and cerebrospinal fluid levels.

Seeking to determine whether the presence of inflammation of the meninges is an important factor in the penetration of penicillin into the

119. McDermott, W., and Nelson, R. A.: The Transfer of Penicillin into the Cerebrospinal Fluid Following Parenteral Administration, *Am. J. Syph., Gonorr. & Ven. Dis.* **29**:403 (July) 1945.

120. Kaplan, L. I.; Read, H. S.; Becker, F. T., and Seymour, C. F.: The Concentration of Penicillin in the Spinal Fluid Following Intramuscular Administration in Neurosyphilis: A Negative Report, *J. Lab. & Clin. Med.* **31**:317 (March) 1946.

121. Dumoff-Stanley, E.; Dowling, H. F., and Sweet, L. K.: The Absorption into and Distribution of Penicillin in the Cerebrospinal Fluid, *J. Clin. Investigation* **25**:87 (Jan.) 1946.

122. Schwemlein, G. X.; Barton, R. L.; Bauer, T. J.; Loewe, L.; Bundesen, H. N., and Craig, R. M.: Penicillin in Spinal Fluid After Intravenous Administration, *J. A. M. A.* **130**:340 (Feb. 9) 1946.

cerebrospinal fluid, Kinsman and D'Alonzo¹²³ performed spinal fluid assays on 2 patients with tuberculous meningitis, 9 with meningococcus meningitis and, as controls, approximately 20 patients with early syphilis without meningitis. In none of the patients used as controls could penicillin be detected in the cerebrospinal fluid. In the presence of meningitis, after large intramuscular doses, penicillin occasionally was found in the spinal fluid, but its appearance was irregular and never in excess of 0.05 units per cubic centimeter. The spinal fluids of 4 patients with meningococcic meningitis were examined after the intrathecal injection of 10,000 units. After eight hours, the spinal fluid contained 3.9 to 20.0 units per cubic centimeter and after twenty-four hours 0.078 to 0.312 unit per cubic centimeter. In the light of this finding, the authors suggest that intrathecal injections of penicillin need not be repeated oftener than once every twenty-four hours.

Since penicillin does not penetrate the subarachnoid spaces in appreciable quantities following extrathecal injection and since its excretion following intrathecal administration is delayed, there might appear to be certain theoretic advantages of the latter route of administration in the treatment of neurosyphilis.

There are, however, certain objections to the subarachnoid administration of penicillin. From the clinic and from the experimental laboratory¹²⁴ have come additional reports of convulsive seizures, signs of meningeal irritation and other untoward reactions following intrathecal use.

That the phenomena are not due to impurities in the preparations used has been shown by Walker and his colleagues,¹²⁵ who have encountered untoward reactions with penicillin made by ten different manufacturers and with purified crystalline penicillin.

Despite these reports of untoward reactions, the intrathecal administration of penicillin has been used by some investigators, and their early results have been reported favorably. Thrasher,¹²⁶ for instance, has made a preliminary report on 70 patients with various forms of neurosyphilis treated by the intrathecal administration of penicillin. The weekly intrathecal administration of penicillin in doses of 20,000 units apparently

123. Kinsman, J. M., and D'Alonzo, C. A.: The Penetration of Penicillin Through Normal and Inflamed Meninges, *New England J. Med.* **234**:459 (April 4) 1946.

124. Miller, L. S.: Intracisternal Penicillin: Observations of Its Effect on Dogs, *J. Pediat.* **28**:671 (June) 1946.

125. Walker, A. E.; Johnson, H. C.; Case, T. J., and Kollros, J. J.: Convulsive Effects of Antibiotic Agents on the Cerebral Cortex, *Science* **103**:116 (Jan. 25) 1946.

126. Thrasher, J. R.: Intrathecal Penicillin in Cerebral Spinal Syphilis, *J. Indiana M. A.* **38**:216 (July) 1946.

was well tolerated, although toxic reactions are not detailed. Weickhardt¹²⁷ expresses the opinion that intrathecal injections of therapeutically effective amounts of penicillin may be given provided that a series of gradually increasing small doses has been tolerated. Gradual elevation of dosage is regarded as a significant factor, small initial doses perhaps serving to "desensitize" neural tissues to the drug. Four parietic patients with no history of convulsions were treated with intrathecal administration of penicillin alone, and favorable results were obtained clinically and at examination of spinal fluid.

Nevertheless, the incidence of untoward reactions plus the necessity of frequently repeated lumbar punctures has discouraged the use of massive doses of penicillin by the intrathecal route. In view of the distinctly favorable results that have been observed after intramuscular or intravenous injection, subarachnoid administration seems undesirable except, perhaps, in certain exceptional cases in which the conditions fail to improve after therapy with parenterally administered penicillin.

Oral Administration.—It has long been known that the oral administration of penicillin is less satisfactory than is parenteral injection. Many attempts have been made to increase the efficaciousness of orally administered penicillin, and special advantages have been claimed for a variety of adjuvants, e. g., various aluminum salts,¹²⁸ calcium carbonate¹²⁹ and triisopropanolamine.¹³⁰ Information is now available, based on carefully controlled experiments by Bunn and his co-workers¹³¹ and by Finland, Meads and Ory,¹³² which indicates not only that there is little to choose among these various adjuvants but also that none has any striking effect in increasing either the height or the duration of penicillin levels in the blood.

127. Weickhardt, G. G.: Intrathecal Administration of Penicillin in General Paresis, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:235 (May) 1946.

128. Welch, H.; Price, C. W., and Chandler, V. L.: Prolonged Blood Concentrations After Oral Administration of Modified Penicillin, *J. A. M. A.* **128**:845 (July 21) 1945. Paul, W. D.; Rhömberg, C., and Wallace, E.: Penicillin by Mouth in Combination with Aluminum Dihydroxyaminoacetate, *J. Indiana M. A.* **38**:298 (Sept.) 1945.

129. Seeberg, V. P., and Collen, M. F.: Calcium Carbonate as an Antacid for Oral Penicillin, *Science* **102**:225 (Aug. 31) 1945.

130. Cutting, W. C.; Halpern, R. M.; Sultan, E. H.; Armstrong, C. D., and Collins, C. L.: Administration of Penicillin by Mouth with Results in the Treatment of Gonorrhea, *J. A. M. A.* **129**:425 (Oct. 6) 1945.

131. Bunn, P. A.; McDermott, W.; Hadley, S. J., and Carter, A. C.: The Treatment of Pneumococcic Pneumonia with Orally Administered Penicillin, *J. A. M. A.* **129**:320 (Sept. 29) 1945.

132. Finland, M.; Meads, M., and Ory, E. M.: Oral Penicillin, *J. A. M. A.* **129**:315 (Sept. 29) 1945.

Bunn's group finds that the height and duration of blood penicillin concentrations observed in fasting serums after oral administration are of the same order of magnitude regardless of whether the penicillin is administered following an antacid, as a suspension in oil, as a suspension in oil mixed with beeswax or in plain water. Also tested were a number of additional vehicles and methods for the oral administration of penicillin, including an oil suspension mixed with shellac, trisodium-citrate tablets, lecithin, mucin, stearates or aluminum hydroxide gel. In no instance was it possible to demonstrate that any method was superior to the oral administration of penicillin in capsule form or dissolved in water. With any of these methods, approximately five times as much penicillin is required to achieve an effective blood concentration when the material is administered by the oral as when it is given by the intramuscular route.

Confirming the findings of Bunn, McDermott and their associates, Finland, Meads and Ory found that an oral dose of 90,000 units of penicillin given one-half hour before breakfast resulted in serum levels comparable with those obtained from 15,000 to 20,000 units given intramuscularly. As compared with serum levels of normal persons, more sustained levels were obtained from oral administration of penicillin, whether given before or after meals, in persons with achlorhydria. The serum levels obtained with ordinary penicillin administered in saline solution were as satisfactory in height and in duration as were those obtained with any of the special preparations for oral administration tested, with the possible exception of the combination of penicillin with aluminum hydroxide gel.

Penicillin levels effective in the treatment of gonorrhea and pneumococcus pneumonia could be fairly well maintained with several oral preparations given every two hours in doses of from 90,000 to 100,000 units. The authors suggest that oral therapy should prove effective in infections in which low doses of parenteral penicillin have proved adequate but that it cannot be expected to be effective against organisms requiring higher doses of penicillin.

McDermott and his co-workers¹³³ state the belief that the lower concentrations of penicillin which are attained in the blood and urine after oral, as compared with parenteral, administration are chiefly the result of a defect in absorption and not primarily due to penicillin lost by acid destruction. A study of the urinary excretion of penicillin after both oral and intramuscular administration was made in 6 patients with complete achlorhydria. The amount of penicillin excreted ranged from 26 to 100 per cent of the total amount injected intramuscularly

133. McDermott, W.; Bunn, P. A.; Benoit, M.; DuBois, R., and Reynolds, M. E.: The Absorption of Orally Administered Penicillin, *Science* **103**:359 (March 22) 1946.

and usually was more than 60 per cent. Following oral administration, the range of urinary excretion varied between 8 and 32 per cent. The authors also were able to demonstrate inactivation of penicillin by incubation with emulsions of stool for twenty-four hours.

McDermott's group¹³⁴ has further sought to trace the fate of orally administered penicillin to find the reason for its relative ineffectiveness by this route of administration. On the basis of extensive experimentation, they conclude:

1. Absorption of ingested penicillin occurs chiefly from the duodenum. The amount of absorption which occurs from the stomach is not established, but is probably small.

2. Inactivation of penicillin as a result of the acidity of the gastric content is conditioned by a number of variables, and on the whole is seldom great.

3. Absorption of penicillin is rapid. The maximum concentrations are attained in the blood within thirty to sixty minutes of ingestion. The subsequent persistence of penicillin in the blood is a reflection of the height of the maximum concentration originally attained, and does not appear to be a result of continued absorption from the alimentary tract.

4. Absorption of ingested penicillin is incomplete. Two-thirds or more of an orally administered dose are apparently not absorbed.

5. Once penicillin has passed through the small intestine only insignificant amounts are absorbed.

6. The penicillin in the intestine which is not absorbed is inactivated by the bacteria in the colon, or, if an excess be present, it is excreted in the feces.

7. The necessity for the use of larger amounts of penicillin by the oral than by the intramuscular route is primarily the result of incomplete absorption and cannot be explained satisfactorily on the basis of destruction by acid or bacterial action.

Fortunately, thus far no one has seriously suggested the routine treatment of syphilitic infection with oral administration of penicillin. Any such attempt would be highly inadvisable, being doomed to failure by the frailties of mankind. Few patients can be trusted to take oral medication with sufficient regularity and over such a prolonged period as is necessary to cure syphilis.

In one of the Cornell "Conferences on Therapy,"¹³⁵ attention is specifically directed toward certain dangers of the abuse of oral administration of penicillin, including the possibility of sensitization of the patient to such a degree that unpleasant reactions may result when more urgent need subsequently arises, and the dangers of self medication.

134. McDermott, W.; Bunn, P. A.; Benoit, M.; DuBois, R., and Reynolds, M. E.: The Absorption, Excretion and Destruction of Orally Administered Penicillin, *J. Clin. Investigation* **25**:190 (March) 1946.

135. Conferences on Therapy: Oral Penicillin, *New York State J. Med.* **46**: 527 (March 1) 1946.

Certainly the increasing use of orally administered penicillin is fraught with grave dangers for patients with syphilis. Self medication and ill advised prescription-authorized oral therapy may well result not only in suppression of the early clinical lesions of syphilis but also in a considerable delay in establishing a diagnosis of syphilis during the period in which the time factor is of greatest importance.

Prolongation of Penicillin Action.

After its parenteral injection in aqueous solution, penicillin is rapidly absorbed and promptly excreted in the urine. If, therefore, therapeutically effective levels are to be maintained in the blood at the site of action, frequently repeated injections are necessary.

Many physicians have sought to prolong the action of parenterally administered penicillin. A complete enumeration of the variously proposed adjuvants and expedients is not within the scope of this review. All of the proposed methods are either absorption delaying or excretion suppressing. Some of the more recently suggested means of delaying absorption include the use of water in oil emulsions,¹³⁶ mixtures of penicillin with aluminum and potassium sulfate¹³⁷ and simple chilling of the site of injection.¹³⁸ Delay in excretion has been attempted by utilization of the antidiuretic effect of ampuls of pitressin¹³⁹ and by renal blockage with benzoic acid.¹⁴⁰

The most successful method of prolonging therapeutically active penicillin levels continues to be the admixture of calcium penicillin dissolved in peanut oil and beeswax, developed by Romansky and Rittman.¹⁴¹

This method has been further studied by its originators¹⁴² and a mixture developed which, after a single intramuscular injection, maintains adequate levels of penicillin in the blood for at least twenty-four

136. Cohn, A., and others: Repository Injections of Penicillin in Water-in-Oil Emulsion: Effect on Gonorrhea, *Bull. New York Acad. Med.* **21**:442 (Aug.) 1945.

137. Bohls, S. W., and Cook, E. B. M.: The Use of Aluminum-Penicillin Mixtures in Maintenance of Blood Levels of Penicillin: I. Intramuscular Injection of Aluminum-Penicillin, *Texas State J. Med.* **41**:249 (Sept.) 1945.

138. Trumper, M., and Thompson, G. J.: Prolonging the Effects of Penicillin by Chilling, *J. A. M. A.* **130**:627 (March 9) 1946.

139. Lich, R., Jr.: A Means of Inducing Oliguresis During Penicillin Administration, *J. A. M. A.* **128**:1161 (Aug. 18) 1946.

140. Bohls, S. W., and Cook, E. B. M.: The Use of Aluminum-Penicillin Mixtures in Maintenance of Blood Levels of Penicillin: II. Combination of Delayed Absorption by the Use of Aluminum-Penicillin and Renal Blockage with Benzoic Acid, *Texas State J. Med.* **41**:69 (March) 1946.

141. Romansky, M. J., and Rittman, G. E.: A Method of Prolonging the Action of Penicillin, *Science* **100**:196 (Sept.) 1944.

142. Romansky, M. J., and Rittman, G. E.: Penicillin Blood Levels for Twenty-Four Hours Following a Single Intramuscular Injection of Calcium Penicillin in Beeswax and Peanut Oil, *New England J. Med.* **233**:577 (Nov. 15) 1945.

hours and persistent urinary excretion over a period of three days. A relatively constant amount of penicillin is absorbed for each cubic centimeter of penicillin beeswax and peanut oil. Within limits, increase of the size of the injection augments the height of the level of penicillin in the blood and increases the duration of its action. Prolongation of penicillin levels in the blood is accomplished by retardation of absorption by particles of beeswax and is related to the potency of the suspended penicillin in terms of Oxford units per milligram. The preparation found most effectual was one containing 300,000 units in 4.8 per cent beeswax by weight in peanut oil contained in 1 cc. Calcium penicillin in beeswax and peanut oil maintains its potency at least nine months at refrigerator, room and 37 C. temperatures. There was no deterioration after twenty-four hours at 56 C. or after two hours at 100 C.

Atcheson and Edmeades ¹⁴³ confirms the fact that penicillin is detectable in the blood stream for prolonged periods following its intramuscular injection in beeswax-peanut oil. The finding that penicillin is present in the urine for longer periods than in the blood stream suggested to these authors that penicillin may be clinically available long after its presence in the blood cannot be detected.

Nichols and Haunz ¹⁴⁴ also have found penicillin in beeswax-peanut oil mixtures to be a practical and effective method of delaying the absorption of penicillin after intramuscular or subcutaneous injection. At least 0.03 Oxford unit of penicillin was maintained in the blood for at least twenty-four hours following a single intramuscular injection of 300,000 units of calcium penicillin in a 4.8 per cent mixture of beeswax in peanut oil. Penicillin-oil-beeswax mixtures were given subcutaneously to 14 of 40 patients. The remaining 26 received it intramuscularly. Mild inflammation at the site of injection was noted in 2 cases in which the mixture was given subcutaneously. Except for slight local tenderness, no reaction was noted when the mixture was given intramuscularly.

Kirby and his associates ¹⁴⁵ have studied the absorption and excretion of penicillin following three hundred and fifty-nine intramuscular and

143. Atcheson, D. W., and Edmeades, D. J.: Blood Levels and Urinary Excretion in Peanut Oil, Beeswax and Penicillin Mixture, *Science* **102**:199 (Aug. 24) 1945.

144. Nichols, D. R., and Haunz, E. A.: Prolonged Action of Penicillin in Mixtures of Beeswax and Peanut Oil, *Proc. Staff Meet., Mayo Clin.* **20**:403 (Oct. 31) 1945.

145. Kirby, W. M. M.; Leifer, W.; Martin, S. P.; Rammelkamp, C. H., and Kinsman, J. M.: Intramuscular and Subcutaneous Administration of Penicillin in Beeswax-Peanut Oil, *J. A. M. A.* **129**:940 (Dec. 1) 1945. Kirby, W. M. M.; Martin, S. P.; Leifer, W., and Kinsman, J. M.: Maintenance of Therapeutic Blood Concentrations of Penicillin for Twenty-Four Hours Following Single Injections of Penicillin-Beeswax-Peanut Oil Mixtures, *J. Lab. & Clin. Med.* **31**:313 (March) 1946.

subcutaneous injections of a commercial penicillin-beeswax-peanut oil mixture containing 4.8 per cent beeswax and 300,000 units of penicillin per cubic centimeter. There were wide variations in absorption and excretion of penicillin. Assayable levels in the blood persisted for from sixteen to thirty-six hours after intramuscular injection and for from twenty to thirty-six hours following subcutaneous administration. Excretion of penicillin in the urine decreased rapidly after the first twelve hours, but small amounts could be detected for seventy-two hours or more.

In 35 patients treated for syphilis with eight daily administered intramuscular injections of 300,000 units each, penicillin could be assayed in the blood twenty-four hours after each injection on twenty of two hundred and seventy-five occasions, or approximately 7 per cent. Results with subcutaneous administration in 25 patients were superior to those following intramuscular injections, both in uniformity of absorption and in prolongation of blood levels. The authors state the belief that, although larger amounts of penicillin are required than with penicillin in saline solution, penicillin-beeswax-peanut oil mixtures provide an effective and safe method of prolonging the action of the drug in the body.

Penetration of Various Tissues.

Cutting and his associates¹⁴⁶ found that after parenteral administration penicillin is fairly uniformly distributed throughout the body (of rats and rabbits) except to the tissues, such as the central nervous system, which have a high lipid content. The major portion of penicillin administered parenterally was rapidly excreted in the urine and a relatively small amount in the bile and saliva. The fate of a portion of the total amount injected is unknown, but presumably it is destroyed in the body.

Penetration of Body Fluids.—The penetration of penicillin into various body fluids has been studied by Ory and his associates.¹¹⁶ Cerebrospinal fluid levels were determined in 18 patients receiving penicillin intramuscularly. After injections of 20,000 to 60,000 units, there was no penicillin detectable in the spinal fluids, although blood levels at the time ranged from 0.06 to 0.9 unit per cubic centimeter. After intrathecal injections of 10,000 or 15,000 units, cerebrospinal fluid levels were at twelve hours mostly between 10 and 40 units per cubic centimeter and at twenty-four hours 0.03 to 5.0 units per cubic centimeter. Penicillin levels in pleural fluids, determined in 5 patients two and one-half hours after a single intramuscular injection of 40,000

146. Cutting, W. C.; Luduena, F. P.; Fiese, M.; Elliot, H. W., and Field, J.: Distribution and Fate of Penicillin in the Body, *J. Pharmacol. & Exper. Therap.* **85**:36 (Sept.) 1945.

units or after an equal amount in divided doses, ranged from 0.03 to 0.22 units per cubic centimeter. Determinations also were made of penicillin concentrations in peritoneal fluid, pericardial fluid and synovial fluid. The results were reasonably comparable one with another and with those for pleural fluid.

Penetration into the Eye.—In studying the penetration of penicillin into the eyes of rabbits, von Sallmann¹⁴⁷ compared the results of subconjunctival injection, iontophoresis and application of cotton packs and found that the highest concentration was obtained in the aqueous humor by iontophoresis and in the cornea and the iris by the prolonged application of cotton packs. The lowest concentration of penicillin in the aqueous humor, the cornea and the iris was observed after subconjunctival injection. Appreciable amounts of penicillin remained in the ocular tissues for about six hours.

Penetration of Amniotic Fluid and Fetal Blood.—Woltz and Zintel¹⁴⁸ have demonstrated that penicillin is present in appreciable amounts in the amniotic fluid and in the fetal blood after the intravenous or intramuscular administration of the sodium salt of the drug to the mother. Concentrations of penicillin in the amniotic fluid were comparable to those of the maternal and fetal circulations.

The Results of Penicillin Therapy.

Early Syphilis.—In the nationwide study of the effects of penicillin in the treatment of syphilis, the major effort of the cooperative study thus far has been to define the usefulness of penicillin in the treatment of early acquired syphilis in adults. From the advent of this program to Aug. 1, 1945, there were 11,589 patients with early syphilis who were treated by the cooperating clinics. Of such importance are the results of this vast and well organized study¹⁴⁹ that its summary is here reproduced:

The following statements are based on the evidence presented in the body of this report, refer to the treatment schedules analyzed and are to be interpreted with the indicated reservations as to the changing character of penicillin:

I. EVIDENCE OF TREATMENT FAILURE.—A. *Total Dosage.*—The cumulative percentage failure at the end of eleven months after treatment varied from 15 per cent (2,400,000 units) and 62 per cent (60,000 units).

147. von Sallmann, L.: Penetration of Penicillin into the Eye: Further Studies, Arch. Ophth. **34**:195 (Sept.) 1945.

148. Woltz, J. H. E., and Zintel, H. A.: The Transmission of Penicillin to Amniotic Fluid and Fetal Blood in the Human, Am. J. Obst. & Gynec. **50**:338 (Sept.) 1945.

149. The Treatment of Early Syphilis with Penicillin, Committee on Medical Research and the United States Public Health Service, J. A. M. A. **131**:265 (May 25) 1946.

B. Combined Drugs.—The cumulative percentage failure at the end of eleven months with a total dose of 300,000 units was twice as great when it was given alone as when it was given in combination with 320 mg. of arsenoxide (42 per cent versus 21 per cent). This combined dose gave the same results as penicillin alone at a total dosage of 1,200,000 units.

The cumulative percentage failure at the end of four months with 1,200,000 units was twice as great when penicillin was given alone as it was when given with 0.6 to 1.0 Gm. of bismuth (5 per cent versus 2 per cent).

C. Duration of Disease.—For long durations of disease the failure rate was higher than for short durations. For a duration of two months or more the failure rate at the end of eleven months was twice that of those treated within the first week of the disease (32 per cent versus 14 per cent).

D. Color and Sex.—There was no evidence of a difference between colored and white races by the end of eleven months. The female failure rate was slightly higher than the male.

E. Reason for Failure.—The failures were considered by the clinics to be relapses in about 85 per cent and possible reinfections in about 10 per cent. There were no appreciable differences in these proportions for different schedules.

II. EVIDENCE OF SERONEGATIVITY. *A. Percentage Becoming Seronegative.*—The cumulative percentage becoming seronegative by the end of the seventh month ranged from about 30 for patients receiving less than 60,000 units to about 50 for patients treated with 1,000,000 or more units on three hour seven and one-half day schedules. Patients treated with 300,000 units of penicillin plus 320 mg. of arsenoxide had an accumulated seronegativity rate comparable to that obtained with the highest dosage of penicillin alone.

For patients on three hour three and three-fourths day schedules these findings were reversed. The group receiving 600,000 units had an accumulated percentage seronegativity of 62, while only 24 per cent of patients receiving 2,400,000 units became seronegative by this time. When these rates were made specific for color and sex, the same results were found. The groups did not differ significantly as to duration of disease. They were, however, concentrated in certain clinics.

B. Clinic Differences for Same Schedules.—A comparison of different clinics handling the same treatment schedules showed definite differences in the percentage becoming seronegative. It was not possible to test whether this factor accounted for the unexpected results for seronegativity with increasing doses in the three hour three and three-fourths day schedules, since there was no single clinic using all three schedules. In view of the differences in clinic results, it is deemed advisable to compare results on seronegativity for different treatment schedules only if there is a general scattering of clinics involved, or if the results from a single clinic can be compared. Where different schedules are concentrated in a few and different clinics, any comparisons may be misleading, at least until the differences arising from laboratory technics are evaluated.

C. Duration of Disease.—For schedule I (2,400,000 units) the percentage becoming seronegative by the end of the seventh month showed a decrease with increasing duration of disease. Those with lesions of at least two weeks' duration before treatment had a cumulative percentage of 70 becoming seronegative by the seventh month after treatment, while those having had the disease for more than eight weeks had a rate of only 38 per cent.

III. HERXHEIMER REACTIONS.—The several treatment schedules differed significantly among one another as to both the incidence and the severity of Herxheimer

reactions. Although these differences were noted, there was no clearcut pattern which could be discerned. The results for different schedules could be accurately compared only if these are scattered generally among the various clinics or, alternatively, if the results from a single clinic employing several different schedules are available for analysis.

No serious reactions occurred in patients treated with any of the twelve treatment schedules reviewed.

In comparison with the magnitude of the nationwide cooperative study of penicillin in early syphilis, the experiences of individual investigations seem greatly overshadowed. Reports of small series of cases have, however, been made by Bell,¹⁵⁰ Leifer,¹⁵¹ Mayne¹⁵² and Schoch and Alexander.¹⁵³

Since the institution of the routine penicillin therapy for early syphilis in the United States Army, thousands of military personnel have been treated with 2,400,000 units in seven and one-half days. According to a recent statement,¹⁵⁴ the failure rate in primary syphilis, including both seronegative and seropositive conditions, has been less than 5 per cent. On the other hand, the failure rate in secondary syphilis has been between 20 and 25 per cent.

In the European Theater of Operations, the results appear to have been more favorable than in the Army as a whole. Here, Pillsbury¹⁵⁵ has evaluated the results of penicillin therapy in 14,000 cases of early syphilis, following the Army-recommended schedule of 2,400,000 units given in sixty intramuscular injections of 40,000 units each at three hour intervals over a period of seven and one-half days. The incidence of clinical relapse is reported as about 1 to 2 per cent, mostly occurring in the first twenty weeks after therapy. The frequency of serologic relapse in seronegative primary syphilis was 1.8 per cent. Penicillin results compare unfavorably in respect to maintenance or achievement of seronegativity with those of intensive arsenobismuth therapy. Data on 792 patients indicate that seronegativity was present six or more months after treatment in 98 per cent of 274 patients with seronegative

150. Bell, N. J.: Penicillin Treatment of Early Syphilis, Rhode Island M. J. 28:884 (Dec.) 1945.

151. Leifer, W.: The Treatment of Early Syphilis with Penicillin, J. A. M. A. 129:1247 (Dec. 29) 1945.

152. Mayne, G. O.: Penicillin in One Hundred Cases of Early Syphilis, J. Roy. Army M. Corps 86:38 (Jan.) 1946.

153. Schoch, A. G., and Alexander, L. J.: Treatment of Early Syphilis with Penicillin, J. A. M. A. 130:696 (March 16) 1946.

154. Status of Penicillin Treatment of Early Syphilis, Bull. U. S. Army M. Dept. 5:1 (Jan.) 1946.

155. Pillsbury, D. M.: Penicillin Therapy of Early Syphilis in Fourteen Thousand Patients: Follow-Up Examination of Seven Hundred and Ninety-Two Patients Six or More Months After Treatment, Am. J. Syph., Gonorr. & Ven. Dis. 30:134 (March) 1946.

primary syphilis, 88 per cent of 271 patients with seropositive primary syphilis and 72 per cent of 111 patients with secondary syphilis. The results of examinations of the spinal fluid were available on 642 patients six or more months after completion of therapy. In none had there been clinical neurorecurrence, and in only 3 were there even minimal evidences of activity in the central nervous system.

Pillsbury states the belief that penicillin therapy is decidedly superior to any previous form of treatment in respect to nontoxicity, completion of therapy within a prescribed period, healing of early lesions and control of infectiousness. On only one score was penicillin inferior to intensive arsenobismuth therapy, i. e., the incidence of persistent seropositivity six or more months after treatment.

Marshall¹⁵⁶ has discussed the use of penicillin for early syphilis in the British army. Among 270 patients with early syphilis treated with 2,400,000 units of penicillin for seven and one-half days and followed for six months, the failure rate was 8 per cent, in contrast to a 2 per cent failure rate in an equal number of patients treated by a twenty day schedule of arsenoxide and bismuth therapy. Treatment with combined arsenoxide and penicillin also has been used and is believed superior to penicillin alone.

Because of the many gaps in the present knowledge of penicillin therapy, it is not yet possible to outline the optimum method for the use of penicillin in the treatment of early syphilis. Nevertheless, certain minimal suggestions for treatment based on information then available have been advanced.⁹⁸

1. When sodium penicillin in aqueous solution is used for the treatment of syphilis in man, injections should be given by the intramuscular route every two to four hours, preferably every two to three hours, day and night around the clock, for a minimum of seven and one-half to eight days. The presence of penicillin K in commercial penicillin, probably in varying and unpredictable amounts for the next few months [as of June 1946], should be compensated for by an increase in individual and total dosage and if possible by a decrease in the interval between individual injections from three to two hours.

The minimum dose of previously produced and at present available commercial penicillin should be, for seronegative primary syphilis, not less than 3.6 million units (ninety injections of 40,000 units each given every two hours or sixty injections of 60,000 units each given every three hours), and for seropositive primary and early secondary syphilis not less than 5.4 million units (ninety injections of 60,000 units each or sixty injections of 90,000 units each).

For a first relapse (including reinfection, infectious or serologic relapse) of early syphilis after previous treatment of early syphilis this course should be repeated plus 360 mg. of oxophenarsine hydrochloride (mapharsen) or an analogue given twice to three times weekly in six individual intravenous injections of

156. Penicillin Treatment of Syphilis in the British Army, Foreign Letters, J. A. M. A. **130**:963 (April 6) 1946.

60 mg. each plus 1,200 mg. of bismuth subsalicylate given twice weekly in six individual intramuscular injections of 0.2 Gm. each. . . .

For a second relapse of early syphilis after previous penicillin treatment the patient should be transferred from penicillin entirely and placed on metal chemotherapy with arsenic and bismuth, preferably by the twenty-six week schedule employed by the Army and Navy (forty intravenous injections of oxophenarsine hydrochloride and sixteen intramuscular injections of bismuth subsalicylate). . . .

In later stages of syphilitic infection in adult (i. e. latent and late) syphilis the minimum dose should be not less than 3.6 million units, and in certain grave late manifestations of the disease, e. g. dementia paralytica, it should perhaps be as much as 10 million units.

2. In the treatment of infants, and in consideration of the gravity of infantile congenital syphilis, the minimum total dose should probably be greater than that advised for use in adults and should range between a total of 100,000 to 400,000 units per kilogram of body weight. In older children the dosage should be adjusted on a unit for weight basis with a minimum dose of 60,000 units per kilogram of body weight (corresponding to the minimum total of 3.6 million units for an adult).

3. Under no circumstances should penicillin in its at present available form be administered orally for the treatment of syphilis.

4. The only presently satisfactory method of absorption-delaying of penicillin is the administration of calcium penicillin in peanut oil-beeswax. Detailed information is not yet available as to the effects of this preparation in large series of patients with early syphilis or with any other stage of the disease. . . . In any stage of syphilitic infection, the average daily dose for an adult should be 2 cc. (600,000 units) and the total duration of treatment from eight to fifteen days or longer, depending on the stage of the infection. For early syphilis a minimum total dose of 4.8 to 6.0 million units of this preparation is advised.

Calcium penicillin in peanut oil-beeswax should not be administered by the subcutaneous route, since under these circumstances the incidence of sensitizing reactions, with giant urticaria and angioneurotic edema, is excessively high.

5. There is evidence, both from the experimental laboratory and from the clinic, that the addition of arsenic (oxophenarsine hydrochloride) in subcurative dosage to a penicillin treatment schedule enhances the therapeutic effect of each drug. A suggested total dose of an arsenoxide for this purpose is 300 to 360 mg. administered in divided intravenous injections of 40 to 60 mg. each over a total time period of one to four weeks. . . .

In view of [the risks of arsenotherapy] . . . and of possible technical difficulties encountered in the administration of arsenic or in the mere prolongation of treatment necessitated thereby, opinion is divided as to the desirability of including this drug in a recommended penicillin treatment schedule. The majority opinion of a group of competent experts is that the results of penicillin alone, in the dosage and time recommended, would be satisfactory in a sufficiently large proportion of patients with early syphilis treated for the first time to justify eliminating arsenic from the original course of treatment, reserving its use for relapsing cases.

6. There is both clinical and experimental evidence to indicate that an insoluble bismuth salt administered intramuscularly in an oil suspension, e. g. bismuth subsalicylate, produces a slowly absorbed bismuth depot which continually releases small amounts of therapeutically effective bismuth for a period of from three to

six months. There is likewise evidence to indicate that bismuth added to arsenic materially improves the results of metal chemotherapy. If bismuth is added to a penicillin or penicillin-arsenic schedule for early syphilis it may be anticipated that the incidence of infectious relapse within the first six to twelve months after treatment will be materially reduced. This is probably accomplished, for the first few months after treatment, by bismuth effect alone. Later relapse is perhaps prevented or minimized by the fact of development of the patient's own immunity. Whether or not bismuth is of value in effecting cure of the individual patient, it should nevertheless be of considerable aid in minimizing infectious relapse and thereby reducing the risk of spread of infection.

If bismuth is employed, the individual dose should be 0.2 Gm. (expressed as the subsalicylate, not as bismuth metal). A total of 1,000 mg. (five injections) given every other day for a total of nine days is unlikely to produce stomatitis except in patients with extremely bad oral hygiene, or renal damage in patients with previously undamaged kidneys. If the total dose is larger than 1,000 mg., injections should be given not oftener than twice weekly.

However, the opinion of a group of experts is also divided as to the desirability of including bismuth with the original course of penicillin in early syphilis. The majority believe, as for arsenic, that bismuth should be reserved for use in relapsing cases.

7. Commercial penicillin in the dosage and by the methods of administration suggested may be advantageously combined with fever therapy by means of induced tertian malaria in any form of neurosyphilis.

8. The use of sodium penicillin in aqueous solution is a hospital and not an office procedure. Injections of a few hundred thousand units given within one or a few days in a doctor's office are to be avoided.

It should be emphasized that these suggestions for the use of penicillin in syphilis represent a combination of medical desirability and expediency. They are based on information at present available, are only tentative, and are subject to revision within the next few months as further information accumulates.

It is also most vigorously to be emphasized that in the adoption of penicillin therapy for syphilis, the eventual value of which will not be determined for several years to come, the physician has a particular responsibility for careful follow-up and frequently repeated post-treatment observation on all patients so treated.

Acute Syphilitic Nephrosis.

Holman and Makovsky¹⁵⁷ report the successful treatment of acute syphilitic nephrosis with penicillin. Tucker¹⁵⁸ also has found penicillin dramatically efficacious in the treatment of secondary syphilis complicated by acute nephrosis and iritis. Being nontoxic to the kidney, penicillin is preferred to metal chemotherapy, which may further damage the renal parenchyma. Barr and his associates¹⁵⁹ also have successfully treated

157. Holman, D. V., and Makovsky, I. H.: Acute Syphilitic Nephroses Treated with Penicillin, New York State J. Med. **46**:520 (March 1) 1946.

158. Tucker, H. A.: Penicillin Treatment of Acute Syphilitic Nephrosis and Iritis, Am. J. M. Sc. **211**:718 (June) 1946.

159. Barr, J. H.; Cole, H. N.; Driver, J. R.; Leas, R. D.; Miller, M., and Strauss, L. G.: Acute Syphilitic Nephrosis Successfully Treated with Penicillin, J. A. M. A. **131**:741 (June 29) 1946.

acute syphilitic nephrosis with penicillin, and they agree that this is the ideal form of therapy, since there have been no reports of renal irritation from its use.

Penicillin Therapy of Neurosyphilis.

Penicillin has also been widely used in cases of syphilis of the central nervous system. The results of therapy in neurosyphilis, as observed in the several cooperating clinics, do not lend themselves readily to amalgamation. So insusceptible of definition are "improvement" and "progression" in cases of neurosyphilis and so widely do clinicians vary in their interpretations of the clinical phenomena involved that no attempt has been made to consolidate reports. Data are available, however, from several of the clinics that have participated in the nationwide study of penicillin in neurosyphilis.

Rose and his co-workers¹⁶⁰ at the Boston Psychopathic Hospital have treated 106 neurosyphilitic patients with penicillin. The majority of the patients also were given concomitant fever therapy, either by inoculation malaria or by fever cabinet, in amounts approximately half that generally considered sufficient. The total dosage of penicillin used was 3,000,000 units (50,000 units per injection for a total of sixty injections). Their report summarizes the outcome in 70 cases followed from four to twelve months. Clinically, 28 of the 70 patients were improved, 37 were essentially unchanged and 5 were worse. The greatest percentage of clinical improvement was noted among the 49 patients with dementia paralytica. The early results of therapy also were striking in primary optic atrophy, since in 5 of their 6 patients with this ocular condition further loss of vision appeared to have been prevented. Repeated examinations of the cerebrospinal fluid revealed a prompt response of elevated cell counts and total protein determinations in most of the previously untreated patients and a more gradual reduction of the Wassermann titer.

An attempt was made to compare the results of therapy with penicillin plus suboptimal fever therapy with those of "adequate" fever followed by arsenical chemotherapy. The comparison suggests that there is little to choose between in the two methods of treatment. The relative safety and the less prolonged periods required recommend the newer form of therapy. Enjoining caution in the interpretation of their results, the authors conservatively conclude merely that penicillin "is an effective therapeutic agent for late neurosyphilis." Their study, however, suggests that the combination of penicillin with short courses

160. Rose, A. S.; Trevett, L. D.; Hindle, J. A.; Prout, C., and Solomon, H. C.: Penicillin Treatment of Neurosyphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* 29:487 (Sept.) 1945.

of fever therapy may significantly improve the prognosis of the patients formerly considered unsuitable for full courses of fever therapy.

At the Mayo Clinic, 100 patients with various types of neurosyphilis have been treated with penicillin. O'Leary, Brünsting and Ockuly¹⁶¹ summarize the results unenthusiastically as follows:

1. The outstanding result common to most of the patients in this series following the use of penicillin was a return of the cell count, protein and gold curve to within normal limits in the studies of the cerebrospinal fluid with reduction of the strength of the complement fixation and titer reactions of the blood.

2. The outstanding clinical effects as noted among patients who had objective and subjective signs of neurosyphilis were a gain of weight and a reduction of severity and frequency of the pains in the legs. The early symptoms of dementia paralytica were not influenced.

3. The patients who had meningeal neurosyphilis were most responsive both clinically and serologically, while patients who had the parenchymatous forms of the disease were helped only slightly if at all.

4. The outstanding serologic results noted were among the patients who had asymptomatic neurosyphilis and who received penicillin intravenously in doses approximating 1,200,000 units in a week, in association with either three spinal drainages or intraspinal treatments (Swift-Ellis type).

5. Penicillin given in combination with fever therapy, either malarial or by means of the fever machine, did not improve the clinical results noted from fever treatment alone.

6. The administration of penicillin by the intravenous, intramuscular or intraspinal route, alone or in combination with fever therapy, both malarial and by machine, leads us to believe that penicillin alone is not capable of controlling the parenchymatous forms of neurosyphilis. However, in cases of meningeal forms of the disease and in those in which there was a high degree of pleocytosis in association with asymptomatic neurosyphilis, the results thus far are encouraging.

7. In occasional cases of neurosyphilis penicillin therapy produces clinical and serologic results that are outstanding. However, these favorable results are noted in only a few cases and often appear when least expected. It is not possible at this time to account for such great therapeutic discrepancies.

Callaway's group¹⁶² has recorded observations on the first 100 patients with neurosyphilis they have treated with penicillin. Classified according to clinical manifestations, there were 37 patients with asymptomatic neurosyphilis, 39 with dementia paralytica, 11 with tabes dorsalis, 7 with tabetic dementia paralytica and 6 with diffuse meningo-vascular neurosyphilis. All, regardless of type of neurosyphilis, were treated with a total of 4,000,000 units of penicillin given intramuscularly in divided doses. Preliminary observations after at least six months'

161. O'Leary, P. A.; Brunsting, L. A., and Ockuly, O.: Penicillin in the Treatment of Neurosyphilis, *J. A. M. A.* **130**:698 (March 16) 1946.

162. Callaway, J. L.; Noojin, R. O.; Flower, A. H., Jr.; Kuhn, B. H., and Riley, K. A.: The Use of Penicillin in the Treatment of Syphilis of the Central Nervous System, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:110 (March) 1946.

follow-up indicate that 60 per cent of this series of patients have shown clinical improvement plus definite improvement in abnormalities of the spinal fluid; 31 per cent, clinical improvement only; 4 per cent, improvement in cerebrospinal fluid unassociated with clinical changes, and 5 per cent, both clinical progression and lack of improvement in the cerebrospinal fluid. Among the 39 patients with dementia paralytica, 22 (56 per cent) were improved both clinically and in respect to abnormalities of the spinal fluid. Of 18 with tabes dorsalis or tabetic dementia paralytica 1 became worse, 5 were unchanged, 5 slightly improved, 8 moderately improved and 7 had complete remissions. Four of 6 patients with syphilis classed as "meningovascular" responded in excellent fashion, and the other 2 also improved. Febrile Herxheimer reactions were frequent, but there were no reactions severe enough to necessitate termination of penicillin therapy.

The results, these workers believe, compare not unfavorably with the early response to fever therapy and are superior to those obtained with the more prolonged, more expensive and more dangerous metal chemotherapy.

A summation of the effects of penicillin alone in the treatment of 283 patients with neurosyphilis at the University of Pennsylvania has been made by Stokes and Steiger.¹⁶³ The most striking effects they observed were on the abnormalities in the cerebrospinal fluid, in which definite improvement was noted in 74 per cent of the patients treated. Improvement in the spinal fluid occurred in 62 per cent of the patients treated for dementia paralytica, 57 per cent of the patients with tabes dorsalis, 60 per cent of the patients with asymptomatic involvement of the central nervous system and 63 per cent of the patients with congenital neurosyphilis. In only 6 patients in the entire series did the spinal fluid become worse. Over-all clinical improvement of some degree occurred in 65 per cent of the patients with symptomatic neurosyphilis, 24 per cent improving decidedly and 41 per cent slightly. Nine per cent of the patients were worse from a clinical viewpoint. Definite improvement is claimed for 30 per cent of patients with dementia paralytica, 31 per cent of those with tabes dorsalis and 17 per cent of those with meningovascular neurosyphilis. The results with primary optic atrophy were inconclusive, but in 2 of 5 cases gastric crises were ameliorated. The disability resulting from Charcot's joints was, as might be expected, unchanged. In the authors' experience, the maximum effect of therapy was manifest within four months, although improvement and ultimate normality occasionally followed an unsatisfactory or atypical early trend.

163. Stokes, J. H., and Steiger, H. P.: Penicillin Alone in Neurosyphilis, J. A. M. A. **131**:1 (May 4) 1946.

Dementia Paralytica.—In Doty, Koteen and McDermott's ¹⁶⁴ series of 115 neurosyphilitic patients treated with penicillin, there were 8 with dementia paralytica. Satisfactory therapeutic results were observed in 4 of these 8 patients during a follow-up period of six to twelve months. With one exception, the observed improvement was not so striking as usually is seen at a comparable interval after malarial therapy. Two patients with advanced paresis failed to improve after 9,000,000 and 19,000,000 units of penicillin respectively. These authors state the belief that although penicillin exerts a definitely beneficial effect on the mental, physical and laboratory abnormalities of dementia paralytica the extent of this beneficial effect, at least with the dosage used, is not so satisfactory as that following inoculation malaria.

Rosanoff and Norman ¹⁶⁵ report results of penicillin treatment in 2 cases of dementia paralytica. The observations are unusually complete, including a battery of psychologic studies, such as the Hartford deterioration and Rorschach tests, as well as pretreatment and post-treatment electroencephalograms. One of their patients received 3,000,000 units of penicillin and was followed ten months; the other received 1,080,000 units and was observed over a period of five months. In both there was definite clinical and laboratory evidence of arrest of the infectious process. The "mental age" of both patients improved after penicillin therapy, and electroencephalographic abnormalities completely disappeared in 1 of the 2 patients treated. Improvement in the observed abnormalities in the cerebrospinal fluid was also evident.

Stern and Campbell ¹⁶⁶ also have found repeated psychologic tests of value in evaluating the response of patients with dementia paralytica to therapy with penicillin and suggest the use of the adult scale for measurement of intelligence and the Rorschach test to reveal abnormalities of the personality.

Jones and Perk ¹⁶⁷ report 6 patients with dementia paralytica treated with penicillin (two courses, each of 2,400,000 units, separated by one month). In all cases, improvement in the abnormalities of the spinal fluid occurred, reduction in the cell count being the promptest and most consistent change. Mental changes were assessed by repeated psychometric tests (Raven's progressive matrices, Shipley-Hartford retreat

164. Doty, E. J.; Koteen, H., and McDermott, W.: The Clinical Responses in General Paresis to Treatment with Penicillin, *Bull. New York Acad. Med.* **21**:434 (Aug.) 1945.

165. Rosanoff, W. R., and Norman, J. K.: Report of Two Cases of Paresis Treated with Penicillin, *South. M. J.* **38**:819 (Dec.) 1945.

166. Stern, J. E., and Campbell, H. M.: Early Effects of Penicillin Treatment of Dementia Paralytica, *Arch. Neurol. & Psychiat.* **55**:266 (March) 1946.

167. Jones, W. L., and Perk, D.: The Early Results of Penicillin in G. P. I., *J. Ment. Sc.* **92**:414 (April) 1946.

scale and the Wechsler-Bellevue intelligence scale). Three patients were improved mentally, 1 was unchanged and 2 became progressively worse.

Acute Syphilitic Meningitis.—Nelson and Moore¹⁶⁸ report additional information concerning a group of 10 previously reported patients with acute syphilitic meningitis treated with penicillin. The remarkable feature of the additional year of observation is that in all 10 patients the reactions of the spinal fluids, originally strongly positive, had become entirely negative. In none had there developed any clinical evidence of neurosyphilis, 1 had had an infectious relapse and serologic reactions of the blood had reverted to negative in 6 of the 10 cases. These results are believed superior to those obtainable with metal chemotherapy in a comparable period. In view of their excellent results with penicillin given intramuscularly, the authors see no necessity for intrathecal administration in cases of acute syphilitic meningitis.

Arachnoiditis with Subarachnoid Block.—In the series of neurosyphilitic patients being treated with penicillin by Callaway and his associates,¹⁶⁹ there have been 2 cases of syphilitic arachnoiditis with subarachnoid block. In contrast to the unfavorable results that have in the past followed the use of other forms of antisyphilitic therapy, definite improvement occurred subsequent to the administration of 4,000,000 units of penicillin.

Erb's Spastic Paraplegia.—As with all previous forms of therapy, penicillin appears, from the report of Tucker,¹⁷⁰ not to offer any real hope to patients with Erb's spastic paraplegia. Two patients who received 3,760,000 and 6,560,000 units of penicillin respectively were unimproved or worse after therapy. Another died of *Clostridium welchii* infection one hundred and ninety-nine days after the first of two courses of 4,000,000 units of penicillin, postmortem examination revealing anterolateral degeneration of the spinal cord, most extreme in the corticospinal tracts. A fourth patient received 10,000,000 units of penicillin concomitantly with malarial fever therapy, with no beneficial effect evident within an observation period of one hundred and twenty-one days. Although admitting that the reported series is small and the duration of post-treatment observation relatively short, the author feels justified in his pessimistic conclusion that commercial penicillin, at least

168. Nelson, R. A., and Moore, J. E.: Acute Syphilitic Meningitis Treated with Penicillin: A Progress Report, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:227 (May) 1946.

169. Callaway, J. L.; Noojin, R. O.; Kuhn, B. H.; Riley, K. A., and Segerson, J. A.: Syphilitic Arachnoiditis Treated with Penicillin, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:231 (May) 1946.

170. Tucker, H. A.: Penicillin Treatment of Erb's Syphilitic Spinal Spastic Paraplegia, *Bull. Johns Hopkins Hosp.* **78**:161 (April) 1946.

in the amounts employed, does not cure nor even arrest the process of this syndrome.

Electroencephalograms before and after Penicillin Therapy.—Callaway and his co-workers¹⁷¹ have studied the electroencephalograms of 38 patients with neurosyphilis before and after penicillin therapy. Their findings agree with previous reports in that no correlation was found between the severity of neurosyphilis and presence or absence of electroencephalographic abnormalities. After penicillin therapy (4,000,000 units in ten days), many formerly abnormal tracings became normal. There was no strict correlation between the clinical results of treatment and improvement in the electroencephalograms. Abnormal electroencephalograms in neurosyphilis are interpreted as the consequences of local cerebral anoxia and of generalized or localized cerebral inflammation. Many of these abnormalities apparently are reversible with penicillin therapy. The authors express the opinion that electroencephalographic tracings are a valuable adjunct in determining the effect of penicillin in the treatment of syphilis of the central nervous system.

Penicillin in Benign Late Syphilis.

Proof that the lesions of benign late syphilis respond to penicillin therapy has been submitted by Dexter and Tucker,¹⁷² who have studied 21 patients with benign late gummatous syphilis. In 18 cases, cutaneous, mucocutaneous or mucosal gummas were present; 4 of the patients had osseous lesions, and 2 had gumma of the liver. The clinical response was uniformly favorable. Cutaneous and mucosal gummas underwent rapid and progressive improvement after penicillin therapy, there being only 1 patient with incipient relapse and 1 with failure of treatment in the entire group. The lesions of both of these 2 patients healed completely after a second and more intensive course of penicillin. Late syphilitic lesions of the skeleton and of the liver appeared to respond favorably.

Penicillin in Cardiovascular Syphilis.

Evaluation of the usefulness of any therapeutic agent in cardiovascular syphilis involves many years of observation. There is, therefore, no information as to the results of penicillin therapy in this late manifestation of the disease. Many writers have cautioned against the use of large doses of penicillin in the presence of cardiovascular syphilis, fearing possible Herxheimer reactions.

171. Callaway, J. L.; Löwenbach, H.; Noojin, R. O.; Kuhn, B. H., and Riley, K. A.: Electroencephalographic Findings in Central Nervous System Syphilis Before and After Treatment with Penicillin, *J. A. M. A.* **129**:938 (Dec. 1) 1945.

172. Dexter, D. D., and Tucker, H. A.: Penicillin Treatment of Benign Late Gummatous Syphilis: A Report of Twenty-One Cases, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:211 (May) 1946.

Dolkart and Schwemlein¹⁷³ report that in 2 patients with cardiovascular syphilis treated with penicillin there developed untoward symptoms (precordial pain, cardiac consciousness and premature systoles) so severe that discontinuation of therapy seemed to them advisable. Whether these were true Herxheimer reactions is questionable.

Penicillin in the Prevention of Prenatal Syphilis.

In the prevention of prenatal syphilis, penicillin has proved spectacularly successful. All writers are agreed that it is a convenient, safe and effective form of therapy.

A report by Ingraham and his associates¹⁷⁴ deals with 49 pregnant women, of whom, at the time of treatment, 26 had manifest early, 19 early latent, 3 late latent and 1 congenital syphilis. Specific therapy during the pregnancy was with penicillin alone, 10 patients receiving a total of 1,200,000 units and 30 a total of 2,400,000 units. The sodium salt was used in all cases, and injections were given intramuscularly at intervals of three to four hours over a minimum of seven days.

At the time of writing, 1 syphilitic infant had been born from among thirty-seven pregnancies which had gone to term, a "degree of success equal to if not greater than that obtained with the arsenical-bismuth regimens at present widely employed." The mother of the baby born with congenital syphilis had been given 1,200,000 units of penicillin for secondary syphilis during the fifth month of pregnancy. Clinical relapse occurred in the mother during the last month, and dark field-positive lesions were present at the time of delivery.

In these authors' experience, the possibility of abortion seemed a definite threat to some pregnant syphilitic women treated with penicillin. They state the belief that this threat may be anticipated and that it may be avoided by reduction of initial doses for forty-eight hours, rest in bed, sedation and temporary cessation of penicillin therapy if signs of threatened abortion are noted.

So successful has the penicillin treatment of pregnant women been in the hands of Goodwin and Moore¹⁷⁵ that they recommend that metal chemotherapy for syphilitic mothers be abandoned and penicillin adopted in its stead. Their series of 33 infants born to 31 mothers treated with penicillin alone for early syphilis includes no infants with prenatal syphilis. They do not concur in the belief that pregnancy exerts any effect in delaying the serologic response. Neither do they share in the

173. Dolkart, R. E., and Schwemlein, G. X.: The Treatment of Cardiovascular Syphilis with Penicillin, *J. A. M. A.* **129**:515 (Oct. 13) 1945.

174. Ingraham, N. R., Jr.; Stokes, J. H.; Beerman, H.; Lentz, J. W., and Wammock, V. S.: Penicillin Treatment of the Syphilitic Pregnant Woman, *J. A. M. A.* **130**:683 (March 16) 1946.

175. Goodwin, M. S., and Moore, J. E.: Penicillin in Prevention of Prenatal Syphilis, *J. A. M. A.* **130**:688 (March 16) 1946.

opinions that abortion is a frequent evidence of therapeutic shock or that great initial caution in treatment is necessary to prevent this untoward reaction. They summarize:

1. The total dose of penicillin should be not less than 2.4 million units administered intramuscularly in aqueous or saline solution at intervals of not less than two nor more than three hours night and day.

2. The total duration of treatment should be not less than seven and one-half days. . . .

4. Following completion of penicillin treatment, the mother must be followed clinically and with quantitatively titered serologic tests at least as often as once a month until delivery (and preferably for the first year after treatment) and at appropriate intervals thereafter.

5. Retreatment with penicillin should be given during pregnancy to the mother if (a) there is evidence of clinical or serologic relapse or (b) the original maternal serologic titer does not significantly decline within three months after treatment.

6. The infant must be followed after birth for a minimum period of three months by means of (a) frequently repeated physical inspections, (b) quantitatively titered blood serologic tests, preferably every two weeks, and (c) roentgenograms of the long bones taken preferably at the first six weeks of life.

7. There is no satisfactory evidence that abortion, actual or threatened, is more frequent during penicillin treatment of the mother than during other forms of anti-syphilitic treatment, or indeed more frequent than the expected incidence of spontaneous abortion in normal women. . . .

8. It is not yet determined whether a woman with early syphilis, treated with penicillin while nonpregnant or during an earlier pregnancy, may be permitted to go through a subsequent pregnancy without treatment. Although 3 women in the present series have delivered normal children in a second pregnancy in which no treatment was given, further experience must accumulate before the point can be decided. Pending further information, a pregnant syphilitic woman previously treated with penicillin, and whether or not this earlier treatment was apparently successful as to the mother's infection, should be retreated with penicillin in each succeeding pregnancy.

Combining in summary the material from the Pennsylvania group and the group from Johns Hopkins University, Goodwin and Moore state:

1. Fifty-seven pregnant women with early syphilis have been treated with penicillin in two university clinics. Sixty infants have been born [alive] to these women . . . only 1 has developed clinical or laboratory evidence of congenital syphilis. In this 1 case, syphilis in the child might possibly have been prevented. The remaining 59 infants are all apparently normal, and 42 of these have been followed for a long enough time after birth to make practically certain of the diagnosis of "no syphilis."

2. These results in the prevention of prenatal syphilis are superior to any heretofore attainable with any method of treatment. . . .

4. It is recommended that in syphilitic pregnant women penicillin be used routinely for the prevention of prenatal syphilis, other methods of treatment being abandoned.

In further reference to the alleged effects of penicillin on uterine activity, Leavitt¹⁷⁶ has reported that among 21 pregnant women treated with penicillin there were 8 who had uterine cramps or bleeding and that 2 of these patients aborted. He also notes that among 206 non-pregnant women there were 17 who began to menstruate during the first day of penicillin therapy.

Speiser and Thomas,¹⁷⁷ however, were unable to find any conclusive evidence of unusual effects of penicillin on the uterus in their review of 156 patients with prenatal syphilis treated at Bellevue Hospital. They also record having given penicillin to over 1,300 women without noting any menstrual abnormality which could be attributed to the effects of therapy. The menstrual cycles of 100 women under treatment for early syphilis with penicillin subsequently were carefully studied, and in only 1 instance was there any alteration from the usual cycle.

Penicillin Therapy of Congenital Syphilis.

Information as to the effectiveness of penicillin therapy in congenital syphilis has accumulated slowly. A preliminary report has been made by Wilkinson, Saunders and Hansen¹⁷⁸ on the results of penicillin therapy in 29 infants and children with congenital syphilis. The doses used were 20,000 to 40,000 units per kilogram given as sixty to eighty divided doses over seven and one-half to ten days. In 13 infants with manifest lesions, the clinical results were satisfactory: cutaneous lesions improved within twenty-four to forty-eight hours and were healed by the time treatment was completed; rhinitis persisted for two to four weeks; osseous lesions healed slowly, and serologic titers decreased progressively. Of 4 children with asymptomatic early congenital syphilis, satisfactory serologic response occurred in 3 following treatment. In late congenital syphilis, penicillin appeared of value in 4 of 6 patients with interstitial keratitis.

Ingraham and the Philadelphia group¹⁷⁹ have treated with penicillin 26 infants with early congenital syphilis. The average age of these children was 3.6 months. All had clinical manifestations of the disease. The dosage of penicillin used was at first comparable to approximately 2,400,000 units for a 150 pound (68 Kg.) adult. Later this dosage was substantially increased. In general, the clinical response was good.

176. Leavitt, H. M.: Clinical Action of Penicillin on the Uterus, *J. Ven. Dis. Inform.* **26**:150 (July) 1945.

177. Speiser, M. D., and Thomas, E. W.: Regarding the Unusual Effect of Penicillin Therapy upon the Uterus, *J. Ven. Dis. Inform.* **27**:20 (Jan.) 1946.

178. Wilkinson, E. E.; Saunders, W. H., and Hansen, A. E.: Penicillin in the Treatment of Congenital Syphilis, *Texas State J. Med.* **41**:401 (Dec.) 1945.

179. Ingraham, N. R., Jr.; Stokes, J. H.; Beerman, H.; Lentz, J. W.; György, P., and Rose, E. K.: Penicillin in the Treatment of the Syphilitic Infant, *J. A. M. A.* **130**:694 (March 16) 1946.

Symptoms and signs of syphilitic infection were noted to improve and abnormal roentgenologic findings seen gradually to regress over a period of months. Of the infants who remained under observation for longer than six months after treatment, 10 (71 per cent) remained clinically normal and were seronegative and 4 were clinically well but still seropositive. In 40 per cent of the infants there developed, in addition to a febrile reaction, symptoms of severe gastrointestinal disturbance. This consisted in abdominal distention, anorexia, diarrhea and occasionally vomiting. In some of the infants these symptoms were present on admission, but almost uniformly they were accentuated after penicillin was started, tending to regress as the therapy was completed. There were 5 infants who died, none of the deaths being attributed by the authors to penicillin. Intercurrent infection superimposed on debility and toxemia from systemic syphilis was the usual cause of death. The paramount importance of expert pediatric attention is stressed. The authors state the belief that larger doses of penicillin given over a longer period will result in a greater proportion of favorable results.

Having observed 22 congenitally syphilitic infants treated with penicillin, Heyman and Yampolsky¹⁸⁰ note that 13 became clinically and serologically well within a period of eighteen months. Four others had persistently positive serologic reactions sixteen months after treatment. There were three deaths in this series and two serologic and cerebrospinal fluid relapses. All deaths occurred in patients with severe infections, and the authors express the opinion that the greatest considerations in the prevention of fatality are adequate nutrition, hydration and the prevention of intercurrent infections.

Neilson and his collaborators¹⁸¹ have treated 39 syphilitic infants and children with penicillin. Of patients in the 23 cases followed from two to sixteen months, 7 were clinically well and seronegative, 6 were clinically well and seropositive in low titer and 10 remained well but persistently strongly seropositive. One fatality occurred, the cause of death being undetermined. In 3 cases, syphilitic periostitis disappeared clinically in approximately one month and serial roentgenographic studies showed complete healing in three months. There was definite improvement in the child's nutritional state during and after penicillin therapy.

The Effect on the Evolution of Syphilis of Small Doses of Penicillin

The widespread use of penicillin in the treatment of gonorrhea has raised several problems with respect to the effect of such therapy on

180. Heyman, A., and Yampolsky, J.: Treatment of Infantile Congenital Syphilis with Penicillin, *Am. J. Dis. Child.* **71**:506 (May) 1946.

181. Neilson, A. W.; Chard, F. H.; Klingberg, W. G.; Hanchett, L. J.; Gabby, W. H.; Rodriguez, J., and Watkins, C.: Treatment of Congenital and of Acquired Syphilis in Infants and in Children by Penicillin, *Arch. Dermat. & Syph.* **53**:625 (June) 1946.

concomitantly acquired syphilis. Since the doses of penicillin usually employed (100,000 to 200,000 units) are sufficient to cause the disappearance of *T. pallidum* from primary lesions previously dark field positive but are subcurative for established syphilis in human beings, it is conceivable that such therapy given during the incubation period of syphilis may delay the appearance of the early lesions, suppress all outward manifestations and result in asymptomatic infection or actually abort the disease. MacKenzie and Wrong¹⁸² suggest that there also may be delay in the appearance of reagin in the blood, an atypical appearance of the primary lesion and difficulty in obtaining positive results on dark field examinations.

At least some of these possibilities appear to have been realized in clinical practice. Leifer and Martin,¹⁸³ for example, found that of 15 patients treated with penicillin for gonorrhea while suffering from simultaneously acquired syphilitic infection penicillin appeared to prolong the incubation period of primary syphilis in 3 and to suppress the early lesions in 8. Derzavis and Bond¹⁸⁴ also have observed that the early lesions of syphilis may be suppressed by small doses of penicillin.

A review of the published reports of cases pertinent to a consideration of the effect of the penicillin treatment for gonorrhea administered during the incubation period of syphilis has been made by Walker and Barton.¹⁸⁵ These authors indicate the danger to the person and to public health of unrecognized syphilitic infections in patients receiving penicillin therapy for gonorrhea and stress the importance of serologic follow-up. In the presence of "reasonable suspicion of co-existing syphilis," it is suggested that penicillin therapy be withheld until a definite diagnosis of the latter disease can be either established or excluded.

The frequency of febrile Herxheimer reactions following the penicillin treatment of syphilis has suggested to Bauer and Egolf¹⁸⁶ that patients being treated for gonorrhea with penicillin in whom there develop reactions such as fever, headache and malaise should be suspected of having a systemic Herxheimer reaction due to unsuspected syphilis. Walker and Barton¹⁸⁵ and Leifer and Martin¹⁸³ attest the validity of this observation.

182. MacKenzie, D. J., and Wrong, N. M.: Some Aspects of Penicillin Therapy in Early Syphilis, *Canad. M. A. J.* **54**:443 (May) 1946.

183. Leifer, W., and Martin, S. P.: Effect of Penicillin on Course of Early Syphilis, *J. A. M. A.* **130**:203 (Jan. 26) 1946.

184. Derzavis, J. L., and Bond, F. T.: Suppression of Early Syphilis by Subtherapeutic Dosage of Penicillin: Report of a Case, *U. S. Nav. M. Bull.* **46**:259 (Feb.) 1946.

185. Walker, A. E., and Barton, R. L.: The Treatment of Gonorrhea with Penicillin During the Incubation Period or Early Phase of Syphilis: A Review, *J. Ven. Dis. Inform.* **26**:241 (Nov.) 1945

186. Bauer, F. K., and Egolf, C. F.: Herxheimer Syndrome Following Penicillin in Unsuspected Syphilis, *Bull. U. S. Army M. Dept.* **4**:239 (Aug.) 1945.

Minimizing the effects of small doses of penicillin (such as those used in the treatment of gonorrhea) on the evolution of syphilis, Cronin¹⁸⁷ points out that it is difficult to prove absence of secondary exposures between the time of the penicillin therapy of gonorrhea and the appearance of the syphilitic lesion and a sexual exposure sufficiently remote in time from any previous exposure so as to render it the probable source of the double infection.

The problem has been approached experimentally by Magnuson and Eagle.¹⁸⁸ These investigators were able to show that small doses of penicillin administered to rabbits at varying intervals during the incubation period of syphilis may either delay the appearance of the primary lesion or actually abort the infection. In general, the smaller the inoculum and the earlier treatment was begun, the greater was the proportion of lesions that failed to develop. The authors summarize their study as follows:

1. The evolution of early syphilitic infection in rabbits was materially modified by the administration during the incubation period of small doses of penicillin comparable to those used in the treatment of gonorrhea in man.

2. Four hundred units per kilogram injected intramuscularly five times at three-hour intervals to a total of 2,000 units per kilogram, a dose which was less than $\frac{1}{32}$ of the amount, similarly administered, necessary to cure an established syphilitic infection in rabbits, either aborted the infection entirely, or significantly prolonged the incubation period.

3. In general, the smaller the inoculum, and the earlier penicillin was administered during the incubation period, the larger was the proportion of lesions completely suppressed, rather than merely retarded.

4. While no asymptomatic infections were observed in the present experiments, many of the delayed lesions were so small that comparable lesions in man might well have escaped detection, resulting in infections "asymptomatic" in effect if not in fact.

5. With the increasing use of penicillin as a primary therapeutic measure in gonorrhea, it is probable that the number of aborted, delayed, or "asymptomatically" acquired syphilitic infections will increase. Patients receiving penicillin treatment for gonorrhea should be kept under close serologic and clinical observation for a period of at least four months and preferably longer to guard against the latter two possibilities.

Untoward Reactions of Penicillin.

Penicillin is a relatively innocuous substance. Reports of untoward reactions following its use have been confined almost exclusively to

187. Cronin, E.: Coincidental Syphilis and Gonorrhea, *Brit. J. Ven. Dis.* **21**:135 (Sept.) 1945.

188. Magnuson, H. J., and Eagle, H.: The Retardation and Suppression of Experimental Early Syphilis by Small Doses of Penicillin Comparable to Those Used in the Treatment of Gonorrhea, *Am. J. Syph., Gonorr. & Ven. Dis.* **29**:587 (Nov.) 1945.

allergic manifestations in the skin. The allergic reactions reported include: (1) urticaria or angioneurotic edema; (2) papular, vesicular or bullous eruptions, sometimes followed by desquamation; (3) contact dermatitis; (4) an Arthus type of response following repeated intradermal injections; (5) a tuberculin-like sensitivity of the skin, and (6) delayed reactions similar to "serum sickness."

Serious reactions were encountered in about 0.5 per cent of the patients treated by Cormia, Jacobsen and Smith.¹⁸⁹ According to these writers, reactions may occur shortly after the institution of therapy, as a result of a preexisting hypersensitivity, or at later intervals, because of developing sensitization. Both early and late reactions may be so serious as to require discontinuation of therapy. Intradermal testing with penicillin is of limited value as an aid to diagnosis and as a guide to further treatment.

The untoward reactions encountered in 124 patients treated with sodium penicillin have been analyzed by Kolodny and Denhoff.¹⁹⁰ Of the total number of patients, approximately 16 per cent had immediate and 7 per cent delayed reactions. No significant relationship was found between the incidence of reactions and previous penicillin therapy. There was no correlation between a past history of personal or familial allergies, previous cutaneous disease, drug intolerance, previous penicillin therapy or reaction referable to it and the incidence of reaction.

Lamb¹⁹¹ has reported the exacerbation of eruptions considered to be epidermophytosis of the feet and tinea cruris during the administration of penicillin. He concludes that this is "due to allergy" from the drug but does not discuss in sufficient detail the possibility that the reaction may depend on the exacerbation of a preexisting fungous infection.

The incidence of delayed "serum sickness" reactions to penicillin is small. According to Gordon,¹⁹² it occurs probably not oftener than 1:1,500 or 1:2,000 in patients treated with penicillin. Characteristic features of 3 cases reported were delay in appearance, fever and tachycardia, severe urticaria, arthralgia and hydrarthrosis, exfoliative dermatitis of the palms of the hands and a self-limited course of seven to ten days. Anaphylactic sensitization in susceptible persons by the penicillin fraction itself is considered to be the cause of this allergic manifestation.

189. Cormia, F. E.; Jacobsen, L. Y., and Smith, E. L.: Reactions to Penicillin, *Bull. U. S. Army M. Dept.* **4**:694 (Dec.) 1945.

190. Kolodny, M. H., and Denhoff, E.: Reactions in Penicillin Therapy, *J. A. M. A.* **130**:1058 (April 20) 1946.

191. Lamb, J. H.: Allergic Reactions During the Administration of Penicillin, *Arch. Dermat. & Syph.* **52**:93 (Aug.) 1945.

192. Gordon, E. J.: Delayed Serum Sickness Reaction to Penicillin, *J. A. M. A.* **131**:727 (June 29) 1946.

An editorial writer,¹⁹³ commenting on the allergic reactions to penicillin, concludes:

Almost all of the reports [of allergic responses to penicillin therapy] . . . lack, in one respect or another, the essential details to provide a complete picture of the source and mechanism of penicillin allergy. The source of the allergen has not been satisfactorily determined. Presumably, it may arise from its presence in the *Penicillium* fungus, in the media, in the chemicals added in the preparation of penicillin, in the interaction between the chemicals and intermediary products, and in the penicillin itself. No concerted attempt has been made to localize the source of this allergen. . . . More complete immunologic investigation of the allergic patients and more extensive animal experimentation are needed to solve the problem of the origin and mechanism of allergy to penicillin.

THE SYNERGISTIC ACTION OF PENICILLIN AND OXOPHENARSINE HYDROCHLORIDE

Eagle and his co-workers¹⁹⁴ have studied the use of oxophenarsine hydrochloride given in conjunction with penicillin in the treatment of experimental rabbit syphilis. The curative doses of penicillin alone and of oxophenarsine hydrochloride alone having been determined, it was found that small fractions of the curative doses of these two spirocheticidal agents were curative when used in conjunction. The two drugs together were so much more effective than either alone that a synergistic rather than a merely additive effect was suggested. The authors say:

1. In early rabbit syphilis, sodium penicillin given intramuscularly twice daily for 4 days cured half the animals at a total dosage of 44,000 units per kilogram, and 90 per cent of the animals at a dosage of approximately 80,000 units per kilogram.

With mapharsen alone, injected once daily for 4 days, the CD_{50} ¹⁹⁵ dose was 2.4 mg. and the CD_{∞} dose, 3.0 mg. per kilogram. A total of 1 to 1.6 mg. per kilogram cured only 1 of 21 animals.

The simultaneous administration of penicillin and otherwise ineffective doses of mapharsen (0.15 mg. per kilogram daily for 4 days), reduced the CD_{50} level of penicillin from 44,000 units per kilogram to 6,100, and the CD_{∞} dose from 80,000 to 32,000.

With somewhat larger but still subcurative doses of arsenical (0.4 mg. per kilogram), the CD_{50} and CD_{∞} dosages of penicillin were further reduced . . . respectively, one-fifty-fifth and one-twentieth the corresponding values in the absence of arsenical.

2. When sodium penicillin was injected intramuscularly 5 times daily at 4-hour intervals for 4 days, the CD_{50} dose was 1,850 units per kilogram, and the CD_{∞} was 8,000 units per kilogram. The concurrent administration of mapharsen in sub-

193. Allergy to Penicillin, editorial, *J. Allergy* **16**:302 (Nov.) 1945.

194. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis, *J. Ven. Dis. Inform.* **27**:3 (Jan.) 1946.

195. CD_{50} = the dose which cures 50 per cent of the animals.

curative doses (0.4 mg. per kilogram daily for 4 days) reduced the CD_{50} and the CD_{90} doses of penicillin to 320 and 1,000 units per kilogram, respectively. These were one-sixth and one-eighth of the corresponding values without arsenical.

3. It follows that penicillin and mapharsen are synergistic in the treatment of experimental syphilis, and may well be similarly synergistic in man. Under such circumstances, small amounts of penicillin supplemented by subcurative doses of mapharsen would be as effective as much larger doses of penicillin used alone. More important, the proportion of treatment failures in early syphilis cases not cured by penicillin alone may be significantly reduced by using mapharsen and penicillin in conjunction.

4. If penicillin and bismuth prove to be similarly synergistic, the optimum therapy for human syphilis may well consist of penicillin, mapharsen, and bismuth used in combination.

The clinical importance of this laboratory demonstration that penicillin and oxophenarsine hydrochloride are synergistic in action is readily apparent. Schedules of treatment in which penicillin is combined with oxophenarsine hydrochloride, a bismuth preparation or both are currently being evaluated in several of the clinics cooperating in the nationwide penicillin study. So significant does the United States Public Health Service consider this development that at its various rapid treatment centers the concomitant administration of penicillin, oxophenarsine hydrochloride and a bismuth preparation now is used routinely.

(To Be Concluded)

News and Comment

Campaign to Combat Heart Disease.—The American Heart Association, Inc., is initiating a nationwide program of public education and information on diseases of the heart, which will call for emphasis on educational work with schools, parent-teachers' associations and other groups concerned with children because of the importance of rheumatic fever and heart disease.

The program will have as its prime purpose the dissemination of educational information to the public in a broad effort to retard the rapid increase of heart disease throughout the nation. Fatalities ascribed to diseases of the heart are greater than the total of the next five leading causes of death, i.e.: cancer, accidental deaths, nephritis, pneumonia and tuberculosis. It is essential, therefore, that the public know more about the significance of blood pressure, infections, overweight, rheumatic fever and other factors which contribute to various types of heart disease.

It is estimated that there are more than 4,000,000 persons in the United States today who have heart disease. Diseases of the heart and blood vessels, including cerebral hemorrhage, accounted for 575,000 deaths in 1944.

According to recent surveys, rheumatic fever and the type of heart disease resulting from it cause almost five times as many deaths as the combined total of deaths from infantile paralysis, scarlet fever, diphtheria, measles, meningitis and whooping cough.

The educational campaign of the American Heart Association will reach its climax during National Heart Week, to begin on Feb. 9, 1947. It is expected that all branches of medicine, pharmacy, insurance, industry and many other groups interested in health and public welfare will cooperate fully.

Supporting and cooperating groups will include the following national organizations which comprise the American Council on Rheumatic Fever of the American Heart Association: the American Academy of Pediatrics, the American Association of Medical Social Workers, the American College of Physicians, the American Hospital Association, the American Medical Association, the American Nurses' Association, the American Public Health Association, the American Rheumatism Association, the American School Health Association, the National Organization for Public Health Nursing, and the National Society for Crippled Children and Adults. The collaboration of the United States Public Health Service, the Childrens Bureau, the National Tuberculosis Association and others is expected.

Local heart associations and affiliated groups in such cities as New York, Washington, San Francisco, Los Angeles, Chicago and Boston will assist in the National campaign.

Convention of the American Academy of Allergy.—The American Academy of Allergy will hold its annual convention at Hotel Pennsylvania, New York city, November 25 to 27, inclusive. All physicians interested in allergic problems are cordially invited to attend the sessions as guests of the Academy without payment of registration fee. The program has been arranged to cover a wide variety of conditions in which allergic factors may be important. Papers will be presented dealing with the latest methods of diagnosis and treatment as well as with the results of investigation and research. Advance copies of the program may be obtained by writing to the Chairman on Arrangements, Dr. Horace S. Baldwin, 136 East 64th Street, New York City, prior to November 10.

Walter M. Brickner Lecture.—The 1946 Walter M. Brickner Lecture, "Problems Relating to the Pathogenesis of Cirrhosis of the Liver," will be delivered by Dr. Arnold R. Rich, Professor of Pathology at the School of Medicine of Johns Hopkins University, on Thursday, Dec. 12, 1946, at 8:30 p. m., at the Hospital for Joint Diseases.

Members of the medical profession are invited.

Book Reviews

The Physiology of the Newborn Infant. By Clement A. Smith, M.D. Price, \$5.50. Pp. 360, with illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

In the introductory chapter of this work the author states that the presentation of the physiology of the nervous system has been omitted intentionally. If this part could be presented as well as the subject matter of this book has been presented, it would be a welcome contribution.

"The Physiology of the Newborn Infant" begins with a consideration of fetal and neonatal respiration. The problem of respiratory movements before birth and the mechanism of postpartum respiration are considered. It may be advisable to mention in a later edition that differences between the values for the fetal and adult hemoglobin have not been attributed to the prosthetic group of the molecule. At the end of the chapter on fetal aspects of respiration there is a clinical summary, just as there is at the end of every chapter. These summaries form one of the most attractive features of the book.

A subdivision of the chapter on neonatal aspects of respiration is devoted to the effects and duration of anoxia at birth. The statement is made that an adult who has failed to breathe or has otherwise been totally deprived of oxygen for seven or eight minutes does not breathe again. In experiments on voluntary breath holding some subjects were able to hold their breath for as long as eleven minutes, and one at least as long as fifteen minutes, without apparent damage. In these experiments a few deep inspirations of oxygen preceded the breath holding. More recently, this period seems to have been prolonged even further.

A chapter is reserved for the circulatory system in its various aspects; another, for the morphology and the peculiarities of blood coagulation in neonatal life. A short chapter is devoted to icterus neonatorum, which is attributed to hemolysis and inadequacy of hepatic function. Metabolism and regulation of heat form the subject of another chapter, in which the author cites the observations of Benedict and Talbot on comparing pairs of contrasting subjects with similar surface areas. One of each pair was a normal infant; the other was a more or less atrophic infant who was poorly nourished and some months older. It would seem somewhat questionable whether the surface area is really similar under such conditions, if one keeps in mind the criticism of Pfaundler concerning the determination of the significant surface area.

In the chapter on the physiology of the digestive tract it is stated that the length of the intestinal tract during infancy is proportionately greater than in adult life. This may be true, although properly performed measurements, such as those which have been made in the adult by passing a tube through the intestinal tract, seem to be wanting. The subdivision on fetal and neonatal digestive secretions shows the scarcity of adequate data. It might be worth mentioning that kathepsin, which acts best in a slightly acid or neutral medium, would be of value in gastric digestion, but, after all, digestion of protein takes place chiefly in the intestine, where it encounters trypsin and the peptidases. So long as starches are not offered for digestion, the need of any amylase is problematic. Even later, it seems that the phosphorylases are more important for digestion of starches as well as for synthesis of glycogen.

A chapter each is devoted to the assimilation and metabolism of specific food substances such as proteins, carbohydrates and fat, and to the assimilation of minerals and vitamins. In another chapter renal physiology is considered. The sex hormones and the suprarenal, thyroid, pancreatic and parathyroid hormones form the subject of another chapter, while the last chapter deals with neonatal immunology. At the end of the book there is a table of normal values. This

table would seem to deserve a better place. The references to the literature appended to each chapter constitute another good feature. On the whole, they have been selected judiciously.

The aim of the author, as seen from this short survey, is a rather ambitious one. He has succeeded so well that the book may be regarded as a "must" for the pediatrician.

An Introduction to Essential Hypertension. By Richard F. Herndon, M.D. Price, \$2.50. Pp. 88, with 7 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

The author of this attractively printed volume has attempted to present concisely the present conception of hypertension. He has succeeded admirably. There is occasional evidence of attempts to define the undefinable, but the attempts are good. The author presents no original work but digests evidence which has been presented by others. It is a very satisfactory digest which is characterized by forthright and forceful statements and conclusions. It is improbable that the physician whose interest in the subject is solely in the treatment of patients with hypertension will derive any more benefit from the volume than from standard textbooks. However, the student, both undergraduate and graduate, teachers and all physicians with curiosity about problems in fundamentals of disease can read it with profit. The author has placed a string through a labyrinth. With it as a guide, the reader can avoid the confusion which is ordinarily his lot when he reads much of the pertinent literature. There is occasionally the fault of oversimplification. The author errs in considering sulfocyanates and thiocyanates as different drugs.

Dr. W. C. Roentgen. By Otto Glasser. Price, \$4.50. Pp. 169. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

Just what qualities go into the production of a fine biography are difficult to define. If one examines, however, such eminent examples of biographic writing as Boswell's Johnson, Southey's Nelson, Lockhart's Scott, Trevelyan's Macaulay and, in more recent times, Harvey Cushing's Life of Sir William Osler, one finds in all a simple direct style, a vivid description of character and an illuminating anecdote which brings the story to life. All these qualifications are present in Glasser's admirable little biography of Roentgen. One's interest is held from the first line, and there is a happy blending of the story of a great man's scientific achievements with his personal life and character. The selection of illustrations is to the point, and the whole volume is prepared in the usual attractive style of Thomas' books.

Modern Management in Clinical Medicine. By Frederick K. Albrecht, M.D. Price, \$10. Pp. 1238. Baltimore: Williams & Wilkins Company, 1946.

This large manual treats of internal medicine in a comprehensive way but more along the lines of a synopsis than of extended discussions of general subjects. There are innumerable outlines for history taking in various conditions, such as allergic disease or gastrointestinal disease, and tables of differential diagnostic points. There are many excellent illustrations. A brief section will be found on any subject, and hence the main value of the book is for reference.

Digitalis and Other Cardiotonic Drugs. By Eli Rodin Movitt, M.D. Price, \$5.75. Pp. 204. New York: Oxford University Press, 1946.

The subject of digitalis has become extremely complicated in recent years through the popularization of modern purified preparations, such as Lanatoside C, Digitoxin and others. A review such as that of Movitt is therefore of great value. The botany, pharmacology, chemistry and clinical use of all the various preparations are thoroughly summarized with comprehensive references to the literature. There are many useful tables and charts and an index.

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